BEFORE THE

UNITED STATES DEPARTMENT OF DEFENSE

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In the Matter of: :

ARMED FORCES EPIDEMIOLOGICAL :

BOARD MEETING :

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The above-entitled matter came on the record, pursuant to Notice, before DR. LEWIS KULLER, President, at the U.S. Army Center for Health Promotion and Preventive Medicine, Aberdeen Proving Ground, Maryland 21010-5422, in the Conference Center Building, on Thursday, October 12, 1995, at 8:20 a.m.

BOARD MEMBERS PRESENT:

DR. LEWIS KULLER, President

DR. MICHAEL ASCHER

DR. JOHN BAGBY

DR. CLAIRE BROOME

DR. JAMES CHIN

DR. GERALD FLETCHER

DR. BARBARA HANSEN

DR. DENNIS PERROTTA

DR. CLADD STEVENS

DR. MARTIN WOLFE

PARTICIPANTS:

B.G. NANCY ADAMS

CDR. DAVID ARDAY

DR. STEVEN JOSEPH

DR. JOHN MAZZUCHI

COL. FRANCIS O'DONNELL

LT. COL. MICHAEL PARKINSON

CAPT. DAVID TRUMP

PRESENTERS:

B.G. NANCY R. ADAMS

DR. DORIS BROWNE

CMDR. WALTER WEISS

DR. JACK HELLER

LTC. STEVEN FINDER

CAPT. TODD WARREN

AUDIENCE PARTICIPANTS:

COL. DANA LONGINE

COL. JOHN GARDNER

COL. GEORGE LEWIS

COL. JOHN BRUNDAGE

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A G E N D A

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P R O C E E D I N G S

(Time noted: 8:20 a.m.)

B.G. ADAMS: As the Commander of the United States Army Center for Health Promotion and Preventive Medicine, it is my pleasure to welcome the members and staff of the Armed Forces Epidemiology Board.

I appreciate this opportunity to host this prestigious meeting and to use this opportunity to market to you what CHPPM can do in a joint arena to support our national military strategy. When we look at Desert Storm, as well as more recent deployments in Haiti, Somalia and Rwanda, it is evident that environmental hazards, endemic diseases and non-battle injuries all produce casualties.

The AFEB and CHPPM are both organizations which have primary roles in pre-deployment, as well as follow-on work during and after deployments. We are relevant to military medicine at all echelons of work, the strategic, operational and tactical levels.

As part of your agenda, you will be

discussing the new role and mission of the AFEB. I hope CHPPM will be a key component of your new role and mission. We need to work together to identify medical threats and to collect the information that documents the problems we face. Already I am quite optimistic that we will continue to work together, since some of my staff, Dr. Jack Heller, Colonel Bruce Jones and Major Mark Rubertone are speakers for this program. These quality people represent the new work for the Center for Health Promotion and Preventive Medicine.

CHPPM is an elaboration of the environmental and occupational health mission accomplished by the Army Environmental Health Agency for the past 35 years. In November, we will inactivate the AEHA and the CHPPM will become the major subordinate command in the Army Medical Command for occupational health, environmental science, epidemiology and disease surveillance and health promotion. Our priorities for mission services will reflect readiness, health risk and/or regulatory or legal considerations.

We are currently working on five products or services which will define our new organization. The first of these, deployment medical

surveillance, will be briefed to you by Jack Heller when he discusses the Persian Gulf Initiative and Deployment Medical Surveillance.

Our second initiative is personal readiness assessment which emphasizes the importance of individual surveillance before, during and after deployments. This initiative is being worked by Colonel Brundage and Major Rubertone, who is on your schedule to talk about Army medical surveillance activity.

The third initiative is the Theater Army Medical Laboratory which can be shortened to TAML. The TAML is a FORSCOM Unit stationed here at Edgewood. The mission of the 5520th TAML is to identify and evaluate health hazards in the area of operations through unique medical laboratory analyses and rapid health hazard assessments of nuclear, biological, chemical, endemic disease, occupational health and environmental health threats.

Our fourth initiative is a preventive medicine readiness hotline to provide timely, comprehensive and current information to preventive medicine staff for both TO&E and TDA units. This service is being designed to be accessed through

phone lines, secure fax and computer links. The hotline is expected to be phased into operation during FY96.

The fifth and final CHPPM initiative is to develop our Center as a strategic and operational organization for health promotion and preventive medicine.

We are focusing on two of three pillars of the national military strategy which show a healthy and fit force and casualty prevention along with casualty care and management.

The bottom line for CHPPM is readiness through health. CHPPM is working to optimize soldier effectiveness by minimizing health risks and incorporating health promotion and wellness into soldiers' lives.

I look forward to a continued working relationship with the Armed Forces Epidemiological Board. I know together our results will produce a health Armed Forces and we will be able to demonstrate to the American people our accountability for the health of the Armed Forces.

DR. KULLER: We're about ready to go, I hope. The first topic today will be presented by Dr. Browne, who deals with the issue of sickle cell

trait testing in the military. And I think everybody has a handout or should have a handout that was prepared regarding the issue. There are some outside if you don't have them.

I'm sorry about having to talk with my back to most people, but -- Colonel Browne.

COL. BROWNE: Thank you.

Good morning. I'm just sort of rushing in from the train.

What I would like to present is some issues that we have related to sudden death in basic military training as it relates to our sickle cell trait policy. And what we are doing is asking the Board to look at the apparent risk or the increased risk of sickle cell trait in our basic military trainees and how it pertains to increased morbidity and sudden death.

And I think the questions that we would like for the Board to look at and make some recommendations for us, are related to whether we should test all military members for sickle cell trait or sickle cell anemia or other abnormal hemoglobinopathies.

And the question is is there really a need; does this testing help to decrease the risk; is it a

cost effective test for all military members; and whether this testing should be done during their initial physical examination or wait until they arrive at their basic training facility.

The question has come up because there is a lack of uniformity in our policy currently. And so what I would plan to do is to give you an overview of what we have and what has happened over the past several years.

So first, I will start by giving you a little definition and information, not knowing where all of you are in reference to sickle cell anemia; talk a little bit about the current policy and the process that's going on; provide you with some data on past studies and reports that have been done; and offer some conclusions and recommendations that were made by our sickle cell working group.

When we look at basically sickle cell anemia or sickle cell trait, which is what this is talking about, we're looking at a hemoglobinopathy. And I think that it is very important for us to consider hemoglobinopathies and not just make it specifically for the sickle cell abnormal hemoglobin, because there is some overlap with other hemoglobinopathies.

What we're talking about is looking at the hemoglobin and that abnormal protein that is in the red cells. And this is the cell that carries the oxygen. And when you have a normal hemoglobin; that is, the A, the A2 and the F, usually the F being the fetal hemoglobin. And as you get older, of course, that decreases in percentage and A being the normal hemoglobin.

We're concerned with the abnormal hemoglobins. S being the one for sickle cell. You can also have an abnormal C or G, to a lesser extent, and also some of the thalassemias. And we would like to have this to deal with all of those abnormal hemoglobin.

When we look at sickle cell, of course, this is an inherited disorder. It produces this abnormal hemoglobin. And then under certain conditions, of course, if you inherit one of these abnormal genes from one parent with normal hemoglobins from the other parent, of course, you will have sickle cell trait. And you can see that the sickle cell trait is apparent in about 8 percent of the African-American population. Thirty-five to 40 percent of the hemoglobin S is usually characteristic in the sickle cell trait population.

If you inherit an abnormal gene from both parents, of course, you then have the sickle cell anemia that is characterized by the SS hemoglobin and of course, you're running in the 80 to 90 percent of abnormal hemoglobin, with a small percentage of A. And of course, as you get on to teenagehood and young adult, you lose that fetal hemoglobin. And of course, in the African-American population, this is less than 1 percent of the overall population in the United States.

When we look at the ability to sickle, this is when the hemoglobin takes on this abnormal shape that is characteristic of sickle cell anemia, this usually occurs in certain conditions. And what happens is that when the hemoglobin takes on this abnormal shape, such as like a sickle or a crescent, it decreases the ability of the cell to travel through the vessels and again, results in some symptomatology that I will discuss in just a bit.

If we look at sickle cell trait again; that is, having one gene that is abnormal and one that is normal, those individuals usually have a near normal life expectancy. However, they may go through a period of time where they are exposed to certain conditions that will result in symptomatology. Such

conditions as high altitude usually greater than 10,000; certain other stressful kinds of situations. And this may result in some small or micro infarcts that may be manifested in the kidney and the spleen and, of course, in blocked vessels.

If you have both of the genes abnormal and you have sickle cell anemia or what is underlined on the slide as sickle cell trait, of course this results in a significant amount of what we consider painful crises. These individuals will go on to have infarcts in various organs and usually do not live to a full normal adult life. Of course, many years ago, they were not living past the 20's and of course now we have a few of them living until age 40.

The greater problem seems to be in the kidneys and in the spleen. And what we're looking at are blocked vessels. This is usually called by small infarcts that result in scaring in the kidneys and it affects the kidney's ability to conserve water. And of course, we know that because the urine is not concentrated.

Of course, this leads to greater problem with volume depletion or dehydration when that mechanism is no longer present. And of course, we

feel that from some of the data that this perhaps contributes to the problem that these individuals would have in the military when they're undergoing their basic training and the rigorous physical training that is required of them.

Since this topic was really looking at the exercise related sudden death, again, just to give you a definition of what we're meaning by sudden death, of course, this is death that occurs with usually a minimal amount or no warning signs. And the individuals just collapse. And even at autopsy they're not able to determine the etiology of that sudden death.

An accompanying condition is called rhabdomyolysis. This is where you have a breakdown or damage to the skeletal muscle tissue in the kidneys, and of course, a leaking of certain cellular components that will then go on to result in acute renal failure as the rhabdomyolysis progresses and ultimate can result in death.

Our policy in DoD started back many years ago. In 1972 we requested the National Academy of Sciences to look at this condition because, of course, it created a great deal of controversy. And out of the review by the National Academy,

recommendations were made that we should screen all accessions. And of course, you would exclude individuals that had sickle cell disease from going on to matriculate in the military.

And, of course, it would put a restriction on flying duties for those individuals with sickle cell trait. And it recommended also that we continue on with some further study.

I will point out that these recommendations of course later on got into a great deal of controversy because it resulted in discrimination against certain individuals that would have the trait.

In 1973, the Services went on to adopt the recommendations that were made by the National Academy. And as I indicated on the next slide, you will see that this resulted in the exclusions of aviation capability for individuals, particularly in the Air Force.

And so the Air Force Academy started to disenroll its cadets in 1979. A great deal of controversy, as I say, resulted in this and there were a number of congressional hearings and debates and of course class action suits resulted in that.

And in 1981, the Services then went on to

allow limited aviation duties for those individuals that would have sickle cell trait. And what they did is put a percentage limit on that abnormal hemoglobin. And you can see that you had to have less than 41 percent of the abnormal hemoglobin to go on to matriculate in the aviation area.

We continued to study this area because we did not have good scientific data. And in 1981, the Uniformed Services started a tri-service study. This was followed up in 1983 by a study done by Walter Reed, a prospective study in conjunction with the Sickle Cell Department at Howard University and their Sickle Cell Disease Center.

In 1985, the Secretary of Defense went on to remove all restrictions based upon the limited amount of data that we had and the hearings and suits, to remove all restrictions from sickle cell trait individuals in terms of their aviation and diving capabilities.

Of course, that ended the studies at that particular time.

The process then was develop that what we should do is that looking at those individuals that are going to enter the military, not all of them are screened as they come through the MEPS center or

through the DoDMERB. They are usually screened at the basic training area in the Navy and in the Air Force, as well as Marines. They are not screened in the Army at the basic training facilities.

And what this requires in terms of the screening is that you do a basic -- a Sickledex test. This is where you're taking some blood and you're looking at the ability of this blood to clot in this screening test. And if that test is abnormal, then those individuals are provided counseling as to the potential risk of having sickle cell trait and the importance of increased altitude and hydration.

Of course, those individuals that are positive are being further tested with a hemoglobin electrophoresis which will then go on to differentiate more definitely the type of abnormal hemoglobin that these individuals would have.

During this screening process, there is not a discussion on sudden death or the consequences of Rhabdomyolysis.

This slide, again, is something that I've already gone over in terms of the Sickledex test. That test is a very inexpensive test and it can be done in the local laboratories; whereas, the

electrophoresis is a much more definitive test and again requires testing in certain specific laboratories that would have that capability.

Right now, those individuals that are coming through our military training and allowed to go on for accession, of course, must have at least a 50 percent of their hemoglobin must be A. That is the normal hemoglobin. They must also have no symptoms of sickling or sickle cell crisis. And if they are allowed to go on to fly, those individuals would have less than 41 percent of that abnormal hemoglobin, no evidence of anemia of any type and no other associated hemoglobin abnormality. And that would be determined by the electrophoresis test.

When we look at some of the past studies that have been done -- and of course we still need a significant amount of work in his area -- there have been numerous not only military but also civilian studies that have been reported. There is a tri-service study where we've looked at over two million recruits starting from 1977 through 1981, and it has a 28 percent greater risk of sudden death in those Africa-American troops that have the sickle cell trait. The mechanism of this, of course, is not known at this time.

There are numerous studies that also looked at Rhabdomyolysis as it relates to sickle cell trait. Again, both in the military as well as the civilian population. And what has been determined out of these studies is that usually you see the Rhabdomyolysis in hose sickle cell trait individuals in association with exertion, where these individuals may have not gone through a particular type of conditioning. It is also associated with pre exposure to a viral illness, usually within a couple of weeks prior to the onset of the Rhabdomyolysis. These individuals would have also some volume depletion in terms of dehydration and may have been exposed to conditions where there are low oxygen tension.

On the next slide, this has one of the studies that looked at exercise-related death in those individuals. And this is inferred heat illnesses because again we're looking at symptoms from these individuals in areas that have a high temperature. And we have wet bulb globe temperature that is greater than 75 and you can see that in the yellow, this is the test that was proven in those individuals that had the sickle cell trait. And you can see that again it's about 50 percent.

And then of course in other cases that we could not make a definitive situation, but again with conditions that would infer heat illness that would increase that percentage of sudden death up to about 89 percent.

And if we looked at those that had sickle cell -- the normal hemoglobin without any S, you can see that that percentage is even less. It's about 15 percent in those individuals that were truly documented and then with an inference rate, bringing that up to about 48 percent. So you can see there is a distinct difference between those that have the abnormal hemoglobin and those that didn't.

Here, looking at again some more data for the risk of exercise-related deaths in the black population, and this is a number of studies. I'd like to just point out that we're looking at relative risk in the last column, and you can see that that comes to about 21 percent in terms of the relative risk for those individuals having the abnormal hemoglobin. And this is calculated from the 22 deaths that occurred in 100,000 recruits with sickle cell trait versus 12 individuals out of a population of 1.1 million with normal hemoglobin.

Since the larger amount of data comes from

the Air Force, we looked at the Air Force experience in basic training from 1985 to 1994. There were 433,000 troops that had been looked at. Out of this about 13 percent represent the black population. And of this, 4600 troops had the sickle cell trait. That is comparable to what we find in the general population for blacks.

Out of this experience, there were 11 total deaths of all causes. Three of those deaths related to individuals that had sickle cell trait. And I have some data that you see there on those individuals, all over 21 years of ago. All of them related to exertion in running for some length, usually a mile or more. And again, one individual, you'll note, that had a viral illness just prior to the onset of Rhabdomyolysis and the sudden death that resulted in those individuals.

Again, when we looked at this and compared with some of the civilian data, this is comparable in those individuals that would have sickle cell trait.

Again, looking at the sudden death per 100,000 troops, again we're comparing those individuals with sickle cell trait, compared to those without sickle cell trait and then looking at

the non-black population. You can see that that is a significant number there.

The overall death rate from all causes, of course, is 2.5. And that's just Air Force data.

When we look at a much smaller denominator in the Air Force Academy data, there were five deaths since 1959. Of course, there was no mention of sickle cell trait in any of those. And of course, none of those individuals were black.

There were three cases of Rhabdomyolysis resulting in some of them requiring dialysis. All three of those individuals that had Rhabdomyolysis also had sickle cell trait and they also had pre-exposure to a viral illness that may have resulted in the Rhabdomyolysis.

What we're looking at in terms of the conclusion is that the relative risk is quite high for sudden death in those individuals with sickle cell trait. Of course, the absolute risk of sudden death is low. The association with sickle cell trait and exercise seems to be related to, again, sickle cell trait exercise and sudden death seem to have some correlation.

We are uncertain from the data that we have now whether a gradual training process will

contribute to also a continuous of sudden death or whether this will decrease the sudden death. We think that conditioning may warrant some increase in terms of survival.

The Air Force data is not any different from that we looked at with the overall tri-service studies. And again pointed out in the conclusion is that viral illness may certainly be quite significant.

Some of the recommendations of course coming out of this is that we're emphasizing hydration and acclimatizing these individuals for their particular training process. And if the temperature is greater than 75 for the wet bulb globe, that vigorous hydration is recommended.

They thought that it also should be important for the troop instructors, the recruit and also for medical personnel, but I think significantly it is for emphasizing the importance of this for your medical personnel so that they can counsel the individuals very early on in terms of the likely complications of having sickle cell trait and going out and doing vigorous training or staying in the military.

And one of the recommendations, again, in

the next slide, out of this group is that we establish the DoD Sickle Cell Trait Working Group. And again, those recommendations are that all recruits, tri-service, should be screened at the time of accession. That the risk of sickle cell trait should be explained to them before they are going on to further matriculate in the military. They should have the option to withdraw from the military at that time if they would like to.

We also need to have further research because, again, we have sketchy data at this point. Further information certainly is required to more definitively respond to this.

It is also recommended that no blood donations should be given or taken from individuals with sickle cell trait until they have completed their basic training. Again, because you put them in an anemic situation resulting in the low oxygen situation and it may precipitate other conditions in terms of greater problems with their ability to continue with their vigorous training.

And that if any individual presents with a viral illness, whether this is viral gastroenteritis, upper respiratory tract infection, that those individuals should refrain from any

exercise or physical training activity for at least greater than one week.

The Sickle Cell Working Group had representatives from the Surgeon General's office, the Tri-Service Military Personnel, Health Affairs and Force Management, as well as the research activity. These recommendations were made to Dr. Joseph and to the service secretaries. And of course, the report was sent forward and the Navy and the Air Force concurred on the recommendations of the Sickle Cell Working Group. The Army made a nonconcurrence in testing all of its recruits and of course resulted in having a further look at this information so that we can bring it to the Board for further analysis and your recommendations.

We feel very strongly that the policy should be uniform throughout the Services for all of our individuals and it is recommended that they train and have that option prior to matriculating in the Service, and given the option to withdraw, if they so choose.

I'll be happy to entertain questions.

DR. KULLER: Questions? Yes. Dr. Chin.

DR. CHIN: Two questions. I might as well as the second one first. Why did the Army -- what

reason did the Army give for nonconcurrence? And the other is the testing policy that we have here says both hemoglobin S and I guess G6PD deficiency testing?

COL. BROWNE: Yes.

DR. CHIN: What was the status of G6PD before this? Was that routine before or is this a new recommendation altogether?

COL. BROWNE: This risk has been there since the '60s. That has not changed. And there has not been a question about the G6PD. So that testing is going on.

The question in reference to the Army, the Army felt that it was not necessary to screen at the basic training level because they have already instituted a program of rigorous hydration across the board in watching those areas and that their trainees are not subjected to some of the conditions that you would find in the Navy and the Marines.

And Colonel Longino, who is the Sickle Cell Working Group Chairperson, may want to elaborate further on this.

COL. LONGINO: The Army's position, I think, is -- you know, everybody has their positions on the sickle cell issue as we went into it, and the

complicating factors Doris really hadn't even mentioned or she's alluded to, I guess. And that's when you get into the issues of is it a racial issue; is it a medical issue; is it a training issue. And it is. That's right.

And some of those we have good data on. In the medical side of the house we have some pretty good data. Dr. Clark, for those of you that know him, he's done a lot of research in the area and he's now at Howard University but he's a retired Army Colonel.

Some of the Services have the same opinions that they had 15 years ago because it was a very big racial issue in the early '80s, late '70s/early '80s, as she showed up there with the cadets in the Air Force Academy. I don't think it's as big of a racial issue today but some people may disagree with that.

The Army position of not testing came from the Sec Def letter of 1985 that said that there'll be no restrictions on sickle cell. Well, the other Services' testing came from that same letter. So the Services have sort of been doing -- how they interpreted that letter back in 1985 determined what they've been doing since then in the testing.

The only problem with the Army and the point I want to get to that we had on the Sickle Cell Group is that we had a really hard time identifying all of the causes of death in Army BMT since 1985. So we weren't real sure how many of them were sickle cell related.

The other problem that we had was that it was hard to relate the deaths with a change in policy at BMT regarding hydration. The numbers you showed up there, for instance, were all numbers back in the '70s up to about '84, '85, '86 time frame and very little data since then.

Well, most of our training practices, especially the Marine Coups, Parris Island has had no problem with the sickle cell trait, for instance. Most of our training practices have probably improved.

We learned from the Israeli wars when Israel lost no troops in the '67 war because the force hydrated and Egypt lost 20,000 to combat casualties because of the dehydration and heat elements. We learned since then. We train our people better. We do the Force hydration. What we don't have is we don't have a corresponding database that says back before we hydrated well and had good

training practices, this is what occurred. Since then, this is what occurred.

Air Force, by the way, on those three deaths, what were your training practices during that time period. And we have some indication, although we can't nail it down, that maybe they were a little lax in the area of hydration and proper heat prevention measures during the time when they had at least a couple of those three deaths.

So that's the issue when you really get down to it. It's training and it's medical and then there's this thing in the background called racial that complicates it sometimes.

So, the problem is the data is hard to identify. You can make your mind up depending on which data you look at and what your background on the issue is. So that doesn't help you any, I know, but that I think sums up what the group found, in addition to the very good overview that Doris provided.

COL. BROWNE: And I might add just one thing. In trying to make it a nonracial issue, the recommendation was to screen all recruit. Therefore, you're not singling out the African-American population. And also, I might point that

certain individuals with Mediterranean backgrounds that also have the abnormal hemoglobins. And so, because it is an inexpensive test to do the Sickledex, it is recommended that all recruits are trained and therefore you eliminate the issue of saying we're only looking at a minority population.

COL. LONGINO: We had kind of a funny incident with that, real quick. The Air Force in about -- oh, in the Spring, maybe April or May, changed their policy to counsel the individuals at training who tested positive for sickle cell trait. And when they counseled them, explained the increased risk that these numbers and data show, and then offered them the opportunity to disenroll at that time and send them home. And this was the first couple of days in BMT.

The first person to be identified with sickle cell trait and accept the option to go home was a blond- haired blue-eyed Caucasian. So everybody threw their hands up then and said, well, those people that were saying test everybody versus test only blacks -- you know, how do you identify a Mediterranean. They could have as high a risk. So it really gets messy.

Good luck with this. I'm glad you have it.

I'm done with it. I'm retired in three weeks, so --

DR. KULLER: Dr. Fletcher?

DR. FLETCHER: I enjoyed this very much. There's one case in the civilian arena in the University of Arizona, looked in on the Department of Medicine on this young man who collapsed suddenly prior to his football practice. Core temperature was normal. No evidence of rhabdomyolysis. And finally, had a ruptured spleen. No evidence of sickling. Nothing. They are still investigating this case. The patient subsequently died. He had a history of a positive sickle cell trait.

So there's something mysterious about this illness. There really is.

COL. LONGINO: Just a couple of weeks ago.

DR. FLETCHER: Yes. Two-three weeks ago.

COL. LONGINO: I cut that out and took it to Patty, a nurse, and said I wonder if this was sickle cell.

DR. FLETCHER: Yes. Hugh Alpert who's head of medicine there said this was a trait. And it's a mystery what happened. There's nothing hematological on the autopsy findings and a very mysterious illness that happened.

COL. BROWNE: And again, this is what we're finding in some of the early studies. It may be interesting to look at his percentage of abnormal hemoglobin.

DR. FLETCHER: Maybe something submicroscopic we don't know about.

COL. BROWNE: Yes. Again, microscopic infarcts.

DR. KULLER: Dr. Wolfe?

DR. WOLFE: Dr. Browne, I think you've said that the Army is routinely testing for G6PD? It's my understanding the Army does not test.

COL. LONGINO: The Army only test right now -- the way I understanding it is that they test after BMT for those individuals who are going to go into the high risk areas; i.e., they're going to be exposed to low oxygen atmospheric conditions, the skydivers, I believe some underwaters. But they do not test prior to BMT.

DR. WOLFE: I've got another point. An awful lot of Army people have been flying to the Persian Gulf and Somalia and elsewhere. Do you have any experience with flying as a risk factor, morbidity or mortality, in people who are perhaps unscreened? I guess many of them are unscreened.

COL. BROWNE: The Air Force data on flying, not necessarily specifically Army data, they have looked at altitudes greater than 10,000. Particularly if your percentage of abnormal hemoglobin is at that 41 percent or greater, then you run the risk of having complications.

DR. KULLER: Can I ask -- what I understand is that the data you've presented showing the rate of 22 per 100,000, 22 cases per 100,000, what was the time period from that? I understand that this is all from way back?

COL. BROWNE: Yes. '75, I think, to '81.

DR. KULLER: And the data on the Air Force, the 43 per 100,000? And the question I have -- I'm not asking exact dates. The question was raised about what the current status is.

COL. BROWNE: These were studies that were done in the '80s.

DR. KULLER: So as I understand it, at the present time you have no idea whether there's any sudden deaths related to sickle cell trait in the military?

COL. BROWNE: Not specifically in the military. There is a study that Dr. Karp published in July of 1994 in the Seminars of Hematology where

it was sort of a review of a number of studies. And of course, I think he has applied to look at the military through one of our granting processes. And I'm not sure whether he received that grant and the study is going on at this time or not, but we certainly recommend that -- at least the Working Group recommended further study.

DR. KULLER: It seemed to me a very critical question. The argument is that with improved hydration practices right now and improved medical practices, preventive medicine practices, that the number of cases or deaths are going down. But of course, when you have a rate this low, you've got to have a lot of numbers, otherwise with confidence limits around 22, with 10,000 it would be 0 or it could be 8.

So the problem basically is knowing what's happening. I would be somewhat concerned about setting up specific guidelines for a relatively rare phenomenon and presuming that there won't be a lot of individuals falling through the cracks in the system given such a rare phenomenon in the sense that when people don't see anything for long periods of time, there's generally a tendency to get away from doing anything because nothing seems to happen

until it does happen.

So it would be interesting to see whether there is any cases occurring now and whether the rate really has gone down.

There are two other questions, though. I know that there's new therapy right now to try and prevent -- this is primarily in sickle cell disease, but it's oral drug therapy, as I understand it. Has some thought been given or is there any potential for the use of -- for some of these at least during training? Is there some thought of investigation? I don't know what the status is. I know it's fairly new.

And the second question related to that is in these individuals who got into trouble, was there any evidence that they have any other associated abnormalities, such as myocardiopathies of various sorts, which also are fairly common -- more common in the Afro-American population? Is there any interaction between sickle cell traits and myocardiopathy? Or also, is there any evidence in the military that they have a similar problem with mark bands or any of the connective tissue disorders in relationship to training?

COL. BROWNE: Starting with your last

question, I'm not aware of association with any of the connective tissue disorders. In reference to cardiological problems, there have been a number of things documented, whether they're cardiomyopathies, arrhythmias, et cetera, that they try to associate particularly with the sudden death situations and sickle cell trait. There's evidence in terms of the documentation for that.

When we look at studies that are ongoing, and I think the Army had pulled some data to look at morbidity and mortality in some of the areas, whether it's cardiac, et cetera, and seeing if sickle cell trait was there. It is usually not documented that the individual has sickle cell trait. In those cases where they have sickle cell anemia, of course, that would be documented on the record, so there's no way to capture that unless they have had prior screening and it's in the records, going back and doing a retrospective study.

DR. KULLER: Dr. Ascher?

DR. ASCHER: Do you know the community experience with this problem in terms of whether there are any numbers from medical providers to tell us whether this is a common civilian problem as well and whether we should be a little more vigorous with

taking our hydration information into the community?

COL. BROWNE: Again, the few studies that have had the sudden death with civilian individuals, usually they are either runner or some other athletic activity that they are participating in. There have the few cases there. But again, it's very sparse and it is looking back at the records to see if sickle cell trait played a role in that.

Again, it's not something that has been looked at often enough so that we can have large enough studies, but there are many studies that have one or two individuals running pretty much the same as what we have in the military.

DR. KULLER: I'd like to point out that we've looked at this. The sudden deaths in Afro-American men in the civilian world are much higher than they are in any other group and there's a fairly large number of these deaths which are signed out as myocardial fibrosis, myocarditis, et cetera. Which means that the pathologist really doesn't know what happened. But if he looks hard enough, he can find some areas of fibrosis in the myocardium. And as far as I know, nobody's really taken a very hard look at how many of these might be related to trait.

I think it's a very good question in the civilian sector. Obviously if it happens during physical activity, at a basketball game or training, it becomes very common. But reality is that these individuals could have viral infections much like the military, basically, then thought that they died from viral myocarditis or viral myocardiopathy of some sort, while maybe the real problem is dehydration, viral infection and sickle cell trait that's just not identified in the civilian sector.

COL. BROWNE: Yes. Again, there's not studies to go back and show those myocarditis or myocardiopathies with sickle cell trait. And that's something that really needs to be done to show if there's a correlation.

The sports studies, again, they have been done in a number of athletes in this country, as well as in other countries with the sudden death.

DR. GARDNER: I'm Dr. Gardner from USIS, I've spent the last six years working with Dr. Karp on hemoglobin studies and a lot of what you saw up there was data from our presentation before this committee -- this Working Group.

The best study, the best data come really from the '77 to '81 studies where through autopsy

review and FIP review all the data were done. Since that time, the Army particularly changed its training program to emphasize prevention of heat illness and rehydration which dropped the number of deaths in the Army dramatically and it basically did not see any sickle cell trait related deaths in the Army much during the '80s at all.

Dr. Karp's recent paper kind of summarized what he's tried to collect from '81 through '86 and at that time there was not many deaths related to sickle cell trait in any of the Services. And there has been no funding -- currently no funding to study the basic training deaths in the military and the data since 1986 really are not yet collected.

And to do these kind of studies is very difficult. You have to study all deaths. The exercise-related deaths are difficult to identify.

For example, at Parris Island in 1991, there was a death attributed to drowning and the autopsy said drowning. The FIP review said drowning. But in review of the eyewitness accounts and the records we found that the recruit swam all the way across the pool, swam all the way back, got 10 feet from the edge and then suddenly just stopped and sunk to the bottom. And both the autopsy and

the FIP review mentioned myocardial infiltration and this was an exercise-related arrhythmia with myocarditis most likely death.

And so this would gone in as an accidental death had you not done this thorough review. And so to do these kind of studies takes an extremely thorough review of every death and identifying those factors of pathologic analysis.

Now the 30-fold excess risk that we're talking about for those with sickle cell trait is in those unexplained deaths, those where you don't have anomalous coronaries, cardiomyopathy or myocarditis but those that are left over. And those deaths are primarily rhabdomyolysis, heat stroke and unexplained sudden arrhythmias.

What brought this subject up was three sickle cell trait related deaths in the Air Force in the last three years, and suddenly the whole thing surfaced again. And that's why the Working Group was reestablished.

COL. BROWNE: And there was also one female death in the Navy last year.

COL. LONGINO: Could I just add on to that? That's a real good point of why the whole issue surfaced again. And really it did not surface from

the medical community or the researchers. It surfaced because a commander, a four-star general down in the Air Force said, hey, wait a minute. We have kids dying here of this sickle cell trait. What can we do to prevent it? And him walking into the Pentagon and trying to come up with a way to do that, initiated the whole research program. I think that's good to keep in mind. I appreciate your mentioning that.

DR. ASCHER: Were those three following the established policy for hydration?

COL. LONGINO: Well, as a matter of fact, like I mentioned earlier, we had some indications that the Air Force reemphasized their hydration program following that. We had some numbers and I don't remember exactly, but basically one Summer, close to where the first two deaths occurred, the black flag days at Air Force basic training, which are those days where the wet bulb temperature is so high and therefore they implement precautions, the number was real low. It was six or eight. I can't remember exactly.

This last Summer we saw it -- '94, even though there was a death in the Fall of '94, in '94 black flag days were either 26 or 28. So an obvious

-- the weather is not that much different in San Antonio from Summer to Summer, an obvious reemphasis on heat prevention.

DR. ASCHER: I do think that if you have a prevention that works, such as this hydration policy, you can't let your indicator of its failure be your deaths, I guess, is the point. You have to emphasize to the commander, whether they're four-star generals or lieutenants that this really has to be done regardless of any indicator system. And you believe it, then you probably should stop the screening and use the hydration.

DR. KULLER: Well, I think that we have to unfortunately because of time, we're going to probably stop. But I do want to say one thing. And it seems to me that the critical piece that's missing from this is the data currently about what's happening to deaths of recruits, both from this trait and from other associated conditions so that one could make a reasonable decision. And I think that Dr. Ascher may be correct in saying they have a successful program for hydration, we haven't seen anything. There's non data that says whether this works or doesn't work. It's essentially anecdotal. It's less advanced.

But when you have such a low rate, you're only talking about four or five cases anyway. I mean, it's not a big problem overall. It's a big problem obviously in terms of people who die but I mean it's a small number of events. So I think it's important that the dataset be updated at least to show what's going on.

Thank you very much. That was very interesting. Unfortunately, we're running behind but I guess we'll be all right.

The next discussion will be on primaquine prophylaxis for malaria, Commander Weiss.

CDR. WEISS: Thank you and good morning. My name is Commander Walter Weiss. I am stationed at the Naval Medical Research Institute in Bethesda, Maryland and I'm here representing the Department of Defense malaria program.

I'd like to present to you data supporting a new indication for an old drug. The old drug is primaquine. It's been around since the 1950s. But we have new data showing that this drug can be used now as a prophylactic drug for malaria prevention in the field.

The questions that I'd like to bring to the Board is, after looking at the evidence I'm going to

summarize today, do you think primaquine should be pursued for further development by the Department of Defense for its use in troops and particularly, what sort of additional data would you require in order to add this drug to the recommended list of drugs form malaria prophylaxis in the military.

I'll begin with some background on malaria. This slide is a schematic diagram of the malaria life cycle. At the top an infected mosquito bites a person and sporozoites travel rapidly to the liver. There, they develop over a period of from seven days up to many months, depending on the malaria species, into liver stage malaria parasites called shizonts.

These liver stage shizonts then rupture and release merozoites into the blood and these merozoites begin infecting red blood cells. There is then a red blood cell cycle of replication that goes on with some of these turning into the sexual forms of gametocytes which can go back and reinfect mosquitos.

Now, drugs that attack the liver stages of malaria have the potential of removing malaria from the body entirely and these are termed causal prophylactic drugs. Unfortunately, none of the

anti-malaria drugs that are currently used act predominantly on the liver stages.

Drugs that act on the red blood cell cycle are terms suppressive. That is, there is still malaria in the body; that is, in the liver, but because all the signs and symptoms of malaria illness occur during the red blood cell infection, a person can remain asymptomatic with undetectable red cell infections but they still have malaria in their livers which potentially could break out later. So those are suppressive drugs.

Now, all the -- as I mentioned, all of the current anti-malarial drugs that we have work on the red cell and typically this means that mefloquine, chloroquine or doxycycline are taken during the period of exposure to malaria but that when a person leaves the exposed area they have to continue taking their anti-malarial suppressives for four weeks. This gives time for liver stage shizonts that are still incubating to come out into the blood and be killed off by the suppressive.

Subsequent to that four weeks, it is now recommended that two weeks of primaquine be taken to eradicate any latent forms remaining in the liver. So we're talking about a total of six weeks of

therapy after leaving the exposed area. This is a major problem to getting compliance. People usually take their drugs when they're actually overseas, but when they come home, they like to stop. And a lot of the malaria cases in the military in recent years have been traced back to this lack of compliance on the post-exposure drug.

There are other problems also with the current anti-malarials. Chloroquine resistance is widespread in Asia and Africa and so the old line drug really is not very useful except in certain geographic locations. Mefloquine, which is the gold standard right now, interacts with cardiac and anti-hypertensive medications and may cause neurologic and psychiatric problems. This has been a particular concern for fliers. Doxycycline has to be given daily and also can call photosensitivity skin reactions and GI problems.

This table summarizes the activity of anti-malarial drugs against Falciparum and Vivax lifecycle stages.

Chloroquine and mefloquine both have no activity against Falciparum liver stages but are active against Falciparum blood stages. Chloroquine and Mefloquine also don't act against the liver

stages of Vivax malaria but do work on the suppressive on the blood stages. Doxycycline has some activity against liver stages but not complete, and in addition has activity against blood stages of both Falciparum and Vivax malaria.

Primaquine is quite different, and we'll get to this in more detail in a minute, but primaquine acts primarily on the liver stages of a disease. It does not have any activity in the usual doses against blood stages of the Falciparum and it also works against liver stages of Vivax, but also has activity against blood stages of Vivax.

I am not going to have time today to go into the extensive animal studies or in vitro studies that support these. I'm going to focus mostly on the human use studies, both in the hospitals in the U.S. and overseas.

A quick note on primaquine pharmacology. It's an 8-aminoquinolone drug. It's well absorbed when given orally. It has an extremely short half-life, four to eight hours. And the drugs does not build up when given on a daily basis.

It is highly tissue bound in the liver and other organs, and this probably accounts for the fact that it works on liver stages. It's mechanism

of action against malaria is not known at the molecular level.

The side effects of primaquine: It causes low levels of hemolysis and methemoglobin anemia in normal persons and it can cause severe homolysis in G6PD deficient persons and this requires screening, although I understand that is somewhat controversial and that there certainly are instances in some population groups when there has been mass dosing with primaquine without screening.

Primaquine also is known to cause GI upset if it's taken on an empty stomach, and this has been a particular concern with anecdotal experience over the years. People don't tolerate primaquine. And in the studies I'm going to show, we particularly examined this in a double blind placebo control condition.

Primaquine's history and current uses. It was studied as a daily prophylactic drug in the '40s and '50s, and I'm going to show you some of that data in a minute. It was dropped basically after chloroquine was found to be effective. Chloroquine being less toxic and can be taken once a week.

Primaquine was part of the C-P, chloroquine-primaquine, once weekly prophylaxis in

troops in Vietnam. The dose there included 45 milligrams of primaquine once a week and 300 milligrams of chloroquine. It was used extensively as part of mass malaria eradication programs in endemic areas because of its anti-gametocyte activity, something which I've not mentioned up 'til now.

Currently primaquine is used for terminal eradication of latent liver stages after leaving malarious areas, and the dose for that is 15 or 30 milligrams daily for 14 days.

Primaquine is a very safe drug. There have been very few adverse reactions reported to the FDA from 1952 to 1994, so we have many years of experience with this drug.

On to data concerning the new proposed application. And now is where I go back to the old data from the 1950's.

The best and most significant paper is by Arnold, published in 1955. I've included this paper in the handout and I'll be showing some data from that now.

He did a three-part study. The first part was to take five volunteers; give them 30 milligrams of primaquine on the day before, the day of

sporozoite challenge and for five days after challenge. The sporozoite challenge was the bite of 10 infected mosquitos. All of these persons were protected against subsequent malaria infection in the blood, whereas all the controls came down.

The second phase of the study was to look at single doses of primaquine and these were either 15 or 30 milligrams of primaquine. Also, lower and higher doses were given on different days after sporozoite challenge.

I'll show you this data in a table from the paper right now.

The top part of this graph shows the results when primaquine single dose is given one day after bite of the infected mosquitos. On the bottom you can see the dose of primaquine; 10 milligram dose, 15 milligram dose, 30 milligram dose, 45 milligram dose. And if you follow on the top, 10 milligrams given one day after sporozoite inoculation protected two of 10 persons. Fifteen milligrams protected four of 10 persons and 30 milligrams protected 10 of 10 persons. Single dose of primaquine now.

If you go and administer this three days after the mosquito bites, one finds it works better.

Ten milligram protects four of 10; 15 milligram protects nine of 10; and 30 milligrams protects nine of 10.

If you do it five days after the mosquito bites it doesn't work at all. And this is before you have any maturation of the liver stages into merozoites which can infect the blood.

The last part of this study was for Arnold to treat persons who had a patent blood stage Falciparum malaria infection with primaquine and he showed that there was absolutely no effect on the blood stages.

His conclusions from this were that primaquine acts on a very narrow time window on the early developing liver stage of the parasite. That if you wait until day five of liver stage development, it's ineffective.

These data were repeated and a smaller study published in 1967 by Powell and Brewer and similar data were generated for plasmodium vivax in a study published in 1959. In that case, persons were given single doses of primaquine either on the day of sporozoite inoculation with plasmodium vivax or three or five or seven days afterwards. Only persons given primaquine on the day of sporozoite

inoculation were protected. Three day and five day and seven day volunteers were not protected.

So all of this is consistent with the hypothesis that this drug is acting only on the early liver stages.

Now I want to move to recent field trials of primaquine as a prophylactic drug. There are three. I'm going to run through them quickly. Again, you have the published reports of these trials in the handouts that I gave you. I'm going to pull some highlights out as we go.

The first was run in Kenya at the USAMR Kenya facility. It was published in July of this year. It was a randomized blinded placebo controlled study. The study population was a 9 to 14 year old Kenya children. These were malaria semi-immune. They'd grown up in the area their whole life. They were screened for G6PD deficiency and approximately 5 percent were dropped from the study on that basis.

The study site was in Western Kenya. Ninety-five percent of the malaria is plasmodium falciparum and there's no plasmodium vivax. The rest being malaria innovali.

There were five arms of the study. There

was a daily placebo, a daily primaquine group, a daily doxycycline group, a weekly mefloquine group, a weekly chloroquine plus daily proguanil group. All of the medications were given with crackers and water to decrease GI side effects.

The number receiving the primaquine was 32; duration was 11 weeks during the high transmission season. Transmission is extreme. People are getting bitten by approximately one to three infected mosquitos every day. And by the end of the study, all of the controls had come down with at least one case of malaria.

The efficacy of primaquine was 83 percent with a confidence interval of between 50 and 94 percent, which was equal to mefloquine or doxycycline.

Let me pull out a table to show that. Basically, although the confidence intervals are fairly wide because of the small numbers in this study, it's possible to see that primaquine, doxycycline and mefloquine all were approximately the same. Chloroquine proguanil was less effective and statistically significantly less effective in this group.

Primaquine was surprisingly well tolerated

and there was no increase in GI or other side effects when compared to the placebo group here which received a vitamin pill.

The second trial I'm going to present was done in Indonesia and was also published this year, 1995. This was not a randomized trial but it was blinded. The study population was adult Javanese men who are malaria naive. These were trans-migrants leaving Java, which does not have malaria, and moving to Irian Jaya, which does have malaria.

There were two arms in the study. Primaquine, 30 milligrams given every other day or 300 milligrams of chloroquine given every week. Again, this was given with either rice or crackers to reduce GI side effects.

The number receiving primaquine was 45; the duration was 16 weeks. The efficacy of primaquine was 74 percent against plasmodium falciparum and 90 percent against plasmodium vivax. And this is in comparison with the chloroquine group because there was no placebo group. The side effects were all less frequent than the chloroquine with the primaquine and there were very few GI side effects overall.

The third study I'm going to present is also done in Indonesia. This is current in press in

Lancet. It is a randomized, blinded, placebo controlled trial done in the same population in Irian Jaya. Adult Javanese men, malaria not immune, again, screened for G6PD deficiency.

There were three arms in this study: primaquine 30 milligrams daily, placebo daily or 300 milligrams of chloroquine weekly. All, again, were given with food.

The number receiving the primaquine was 43. The duration of this was one year. So these people took daily primaquine for one year. The efficacy of primaquine compared to placebo now was 94 percent against plasmodium falciparum and 90 percent against plasmodium vivax. The side effects I'll show you right now, but were minimal.

I should point out that there was asymptomatic methemoglobinemia at the end of the study ranging from 1.4 percent to 13 percent but the questionnaire showed no effects of this on exercise tolerance in these men.

Here's some of the supporting data from the study. At the end of the one year prophylaxis period, comparing the placebo groups with the primaquine groups, all of these laboratory tests -- hematologic, renal function, liver function, there

was no differences. And looking at symptoms in the placebo versus the primaquine groups here, there was no increase instance of vomiting, diarrhea or stomach pains.

One finding of statistical significance was an increase in cough in the primaquine group over placebo. This was found only at the end of the study when the analysis was done. The medical monitors during this study did not notice any increased cough or respiratory problems and this may just be a statistical artifact based on the number of questions that were asked.

Based on this data, we are proposing a new indication for primaquine; that is, a prophylaxis of P. falciparum and P. vivax malaria. We are proposing that the dose be given 30 milligrams daily during the period of malaria exposure plus two days for a maximum of 30 days. The two days are for that mosquito that bites the person on the last day that they're in the exposed area.

Potential prophylactic that uses primaquine would be -- daily primaquine could be taken as the sole prophylactic drug for malaria exposure less than 30 days, no antimalarial drugs would have to be taken after the malarious area. So you can get rid

of this whole compliance problem afterwards.

For longer malaria exposures, weekly medications are convenient. However, daily primaquine could be used in addition to the weekly medications for the last 30 days in the malarious area, which would remove the need to take any medications after leaving. Again, we'd get rid of our compliance problem.

Several issues have come up in our working discussions in terms of further development of primaquine and I want to bring these to the Board's notice.

Current labelling of primaquine is 14 days of 15 milligrams daily, although quite commonly it's given 30 milligrams daily because of failures of the 15 milligram regimen. To increase this to 30 milligrams daily for 30 days, the FDA must approve safety and efficacy. We feel fairly confident we can do that, given the 40-year history of primaquine use. We also have 30-day animal toxicity data already.

The second point has to do with a new drug under development. WR238605 is a second generation primaquine-like drug with a longer half-life. If it passes clinical and field testing it would probably

replace primaquine in the future but this may be years away.

So one of the issues in dealing with primaquine is here we have a bird in the hand, something that we know is safe, that we have a lot of experience working with. And we feel that we could probably get a label change with fairly little expenditure of time and money. However, in the future, there may be a second improved drug which will have better pharmacokinetics than primaquine.

Thirdly, the hospital challenge studies I showed you indicate that primaquine works against liver stages and can be stopped after exposure. However, the three field studies to date have shown that it's a prophylactic drug but they weren't designed to show that primaquine can be stopped after exposure. In order to do a study like that, you need to be able to remove the population from the malaria exposure and follow them. That has been very difficult to do.

So, I'd like to leave you with these questions. Should daily primaquine be further delivered for use in troops as a prophylactic regimen against P. falciparum and P. vivax malaria? Specifically, should we pursue the studies now to

get a label change approved by the FDA?

Is there sufficient evidence that primaquine's mechanism of action against the liver stages induces sterile protection and that anti-malarials need not be taken after the exposure period? Specifically, we have the hospital challenge studies which show a mechanism of action against liver stages but not against blood stages. But do these need to be repeated since they are so old? And specifically, do they need to be repeated in the plasmodium vivax case?

Secondly, should new field studies of primaquine prophylaxis be done designed to show that the drug can be stopped two days after the last exposure? That is partly by moving subjects out of the malarious area and following them afterwards.

Thank you very much.

DR. KULLER: We have a few minutes for questions.

Dr. Wolfe.

DR. WOLFE: Assuming that the questions that you pose which is on efficacy are answered, I still have quite a bit of concern about side effects which you're not even asking us about here.

Assuming again that you're going to be able

to test everybody for G6PD, you're probably going to find something, as I understand it, that 12 percent of American blacks are going to be deficient with the A minus variant. They've been shown to be able to tolerate 45 milligram a week but I don't know of any studies that show how they would tolerate 30 milligrams a day. So that's another issue we're definitely going to have to address.

The GI intolerance could be a problem. You admittedly under very controlled studies were able to give these people, small numbers of people, crackers and water and then give them the pill. If you're going to be dealing with hundreds of thousands of troops who maybe even if they want to can't take any food, they're liable to be faced with GI intolerance.

And I have another concern about any combined use of primaquine with mefloquine or doxycycline or even chloroquine, though it's been used in the past. If you go back to the Vietnam experience when chloroquine and primaquine were used and then adapsone was added, you had these deaths from methemoglobinemia. So again, you're going to have a lot of work to do to show that you're going to be able to combine primaquine in that dose, which

in itself may be dangerous with other drugs that have their own side effects; GI, psychological and otherwise.

DR. CHIN: Is pregnancy still a contraindication for the use of primaquine?

CDR. WEISS: There have been no studies that I know of on that, but the feeling is because the G6PD status of the fetus is not known and primaquine probably does cross the placenta, it's not wise to prescribe it.

DR. CHIN: I see.

CAPT. TRUMP: Captain Trump with the Navy.

First, I just want to thank Colonel O'Donnell for his help in getting this on the Board here at the last minute.

The other is what we're asking today is basically questions about what the science shows just on the operational side. A drug like primaquine certainly is attractive. At least for the Navy, when we deal with port visits, ships pulling into a port for a few days, the challenges of giving malaria prophylaxis daily for that period in port is a lot different than trying to look at do we decide to start a multi-week program of

compliance after they have left that area of risk.

So, at least from the operational side, this looks attractive. Obviously, we would like to know that the science supports that at least there's another drug, certainly not a replacement for doxycycline, mefloquine for any of our military operations. And right now we have to deal with these multiple drugs also when you make a decision to start malaria prophylaxis. Obviously, because of your tolerance of the different agents, you have to use multiple regimens for any group of people going into a malarious area. This would just be another drug for us to consider.

So I appreciate your looking at the question and giving us your input.

DR. KULLER: I think Dr. Wolfe made a very critical question though which I think we got a complete answer. And that is, if G6PD testing is not done routinely and you don't know who's G6PD deficient, then you have a problem.

We heard a little bit before that it was unclear whether G6PD testing was or was not being done in the military. If obviously we only go into a port for a couple of days, the idea of suddenly having to test everybody for G6PD --

CAPT. TRUMP: Navy and Marine do G6PD testing along with sickle cell testing at accession. It's documented.

DR. KULLER: And let's say -- does the individual have that on a card with him or somehow so you know if they're on a ship and they go into a port and they start using primaquine.

CAPT. TRUMP: It's in their medical records, sir. And the same folks who would start the prophylaxis have the medical records.

DR. KULLER: They would have the record and the data would be right there. So there'd be little likelihood of a big time mix up.

DR. WOLFE: But operationally are you going to be able to exclude 12 percent of your population and that disregards the Orientals, the Middle Eastern people who have even a potentially more serious G6PD deficiency, you haven't addressed any of this. And it's conceivable you've got 15 or 20 percent of your people if you're doing G6PD deficiency testing that unless you're able to study the effect of the drug, which is going to be a long complicated process, you're going to eliminate them. So I see this as a major drawback to the use of this drug.

CAPT. TRUMP: It goes back to the point I was trying to make before, which is that right now we have people who -- doxycycline may be the drug of choice but they cannot tolerate doxycycline, so we have to use mefloquine. If we have people who can't tolerate mefloquine, we have to go to doxycycline.

We have to use the drugs we have available and primaquine would just be another one that looks attractive. Again, I don't think we're going to be in an position to say that this is one drug is the only prophylaxis we're going to use for even all the ship's company. It's just going to be another drug in the group that we could consider. And as a result, issues about G6PD intolerance, then those folks would have to go on doxycycline, go on mefloquine.

DR. WOLFE: Yes. I think our thinking is that this would be one more string in the bow, given a medical officer trying to make a difficult prophylaxis decision.

COL. LEWIS: Colonel George Lewis. I'm a Commander of the U.S. Army Medical Material Development Activity and we are the principal developer of drugs and vaccines in DoD.

The Board's recommendations are of course a

very powerful tool and lever that has been often used to say, well, the Board has recommended this. This has been approved. Therefore, put the resources towards this.

In this day and time of less field sites and less money and people, and at the same time a considerable emphasis, appropriately, to have a standard amongst Army, Navy and Air Force of a drug or a treatment for sickle cell anemia or whatever, there is tremendous pressure put on what is now a formal development system that the Navy, Army and Air Force to some degree participates in a number of drugs. Again, one of those was pointed out a while ago.

These are ongoing programs. We formally work and informally work with FDA constantly. The Board's wisdom has already come out on a number of studies that would have to be done. Similar studies are being done with other drugs in the pipeline.

So I'm just asking to consider and possibly ask for a view or information of what the whole program is and where this might or might not fit in and how it may or may not compete for these valuable resources. Azifromycin is one that's ongoing in the same area. And there's only so many physicians and

so many people in the area and this would be a tremendous commitment of resources.

So before you make a strong recommendation, you might want to be aware of other arenas.

DR. WOLFE: Yes. I would concur with that. I think that -- I mentioned WR238605 is a major innovation which would probably make primaquine obsolete if it comes to fruition sometime in the future. But primaquine does have this unique ability to attack the liver stages which is not present in azithromycin or palofantrin or many of the other drugs that are also being studied now.

DR. KULLER: Can I ask one last question? What is the magnitude of the problem that we're talking about now in terms of the issue of how much malaria is actually occurring among troops after they get out of the area. As you pointed out, the problem is failing to continue to take prophylaxis.

Are we talking about 100 cases a year or 10 or 5?

CDR. WEISS: Well, recently after -- I mean, people here probably know better than I, but recently after the Somalia operation there was an outbreak at Ft. Drum with approximately 100 cases, I think, in all. And most of those were traced back

to not taking the drugs properly after leaving Somalia.

DR. WOLFE: But they were not recommended to use the drug with that initial cohort of cases. Nobody was taking primaquine because they thought the incidents of vivax was so low. And I think you'd have to look at the subsequent groups, once it was recognized that primaquine was indicated, how many of those complied with this use.

LTC. FINDER: Could I make a quick comment here, please? I'm Colonel Steve Finder from Fort. Sam, in the PEC, the Pharmacoeconomics Center. I'm here today because we're going to talk about typhoid vaccine later this morning.

The reason I want to make a comment here is I think there's a lot of -- the military is very good for having different arms to do different things and oftentimes don't talk to each other. There's a new Board of Pharmacy which is now I guess the DoD proponent for pharmacy policy. At the same time, the PEC is actively involved in doing pharmacoeconomic research looking at these kinds of questions dealing with malaria. Like what is the most cost effective drug to use. And perhaps that's the one we should start with.

And I think it's a good opportunity to do some cross-collaboration. I think it would be worthwhile for perhaps the AFEB. And I think you should look rightfully at what is the right choice from a clinical point of view, but it may be worthwhile looking at the question from an economic point of view. And that's where the PEC perhaps can come in. And it wouldn't be perhaps a good idea to ask the PEC to look at this question specifically and come back to the AFEB and say now of the four drugs or five drugs that are available out there, which is the one most cost effective, or which are the most cost effective in which situation.

And that may be a worthwhile way to kind of resolve some of these question you're dealing with. Given the resource limitations and the fact that a large percent of the population may be G6PD affected, is primaquine really cost effective versus say mefloquine or doxycycline. And the question may turn out to be that it's not, but it is perhaps a tertiary drug and that puts a position for that drug in the whole material of malaria prophylaxis, at which point then pharmacy policy can be developed as to what kind of medication should be carried in our pharmacies. Just wanted to make that little point.

CDR. WEISS: Yes. I haven't gotten into the economics of this at all. Primaquine at this point is off patent. It's a generic -- potentially a generic drug. It's still made by Sinophy Winthrop. But the cost is far less than mefloquine and even less than doxycycline. But I didn't want to get into that really.

DR. ASCHER: Back to the operational question a little bit. How do you do the terminal prophylaxis with primaquine after people come back in the face of the G6PD question? How is that operationalized? With difficulty.

CAPT. TRUMP: With difficulty. It depends on the situation but we either use the two weeks of 15 milligrams daily for prophylaxis or I think it's six weeks of 45 milligrams on a weekly basis as part of the terminal prophylaxis.

DR. ASCHER: How do you fold the G6PD information into that?

CAPT. TRUMP: I think the evidence that Dr. Wolfe had mentioned is that the 15 milligrams daily appears to be tolerated. At least the medical officer is supposed to be aware of the G6PD status. Just monitor the patient or make the patient aware if there's any problems while taking that they seek

care.

I think the evidence was pretty good from 20 and 30 years ago that the weekly primaquine as part of the chloroquine-primaquine combination as a terminal prophylaxis was well tolerated by a vast majority of people.

DR. ASCHER: So the information really isn't used.

CAPT. TRUMP: Which information?

DR. ASCHER: G6PD because the regiments don't stress it.

DR. WOLFE: The Army doesn't even have that.

CAPT. TRUMP: Right. The information --

DR. ASCHER: Your information you're obtaining isn't functionally used. That's what I'm saying. You know the information but when you're post-exposure, you're post-exposure safe in the presence of G6PD, so you really don't use the information.

CAPT. TRUMP: We use it if the option is to go with the two weeks at 15 milligrams daily and even for the others. It is a piece of information for the clinician to be at least aware and to raise their index sufficient if they're going to prescribe

primaquine that even though we think it's safe, be aware that this person may be a higher risk.

LT. COL. PARKINSON: From the Air Force perspective, one of the things that I've found -- and we've tried to stress in some of our post-deployment messages is that flight surgeons and generally public health officers have to do a good job of assessing what was the real risk while the person was in theater because I think massive overuse of primaquine routinely in terms of road orders, exposing large numbers of people when we relatively had a small amount of risk while in theater is something that we want to avoid.

So we've tried to stress that -- you know, verify the degree of risk. Use your in-theater surveillance information to determine whether or not people had exposure to insects, nighttime activities, before you blanket and say everybody should be on terminal primaquine.

The other issue is with G6PD and that whole area. It seems to me like a lot of the research on G6PD and its relationship to primaquine and other types of drugs that cause that has really kind of turned off. I don't know when it stopped. But G6PD, like most things, it's not an absolutely yes

or no contraindication and there are degrees of risk. It's a genetic trait just like other things. And somewhere in this, the G6PD as an issue perhaps needs to be serviced. It cuts across the first question on hemoglobinopathies and we in the Air Force also screen everybody. It's notated in the chart. But it is not an absolute contraindication using the drug.

We have a high threshold for saying if you've got somebody, make sure the person really was exposed. Because if not, you don't want to be blanketly prescribing this drug.

DR. KULLER: I think because of the time we're probably going to have to go on because we have a visit now, I think.

Colonel Brundage?

COL. BRUNDAGE: My name is John Brundage. I'm the Director of Epidemiology and Disease Surveillance. And one of the things I'd like to explain to you is the stratified non-random design for the site visit that we're going to use this morning.

(Laughter.)

We're running a half an hour late, so what I was doing in the back was making on-the-fly

adjustments because what we did not want to do is to cut into either the lunch break or the coffee break.

What we had set up were three sites. And since there are three sites, everybody could not go to all three. The three sites that we're offering to show you are the M83 Fox vehicle which is a vehicle that's being developed by the Chemical Corps which is designed to do reconnaissance on the battlefield, to detect and do initial identification of biological and chemical agents.

Obviously that capability on the battlefield has implications for how, for instance, real time medical surveillance will be conducted by medical departments. And there will be a demonstration of that, a briefing about that, and perhaps some discussion about how that capability fits in with medical capabilities.

It's set up to our right. Through the break area, there is a large concrete pad and that vehicle is set up there and there will be a briefing available.

The second thing that we have set up is a tour of the Chemical De-Mil Training Facility. As I think everybody knows, there's large arsenals of chemical weapons that are stored and because of

treaties and other obligations those need to be properly demilitarized and disposed of.

The training for that operation is conducted here. There is a mock-up of the facility and a briefing that walks individuals through the facility and talks about exactly what happens when that process occurs. That's about half a mile over from here and that takes about 45 minutes or an hour.

The third thing this afternoon you're going to hear a briefing from Dr. Heller about mapping the battlefield, if you will, with environmental threats, that then gets interpreted based on troop locations. Real time medical surveillance on the battlefield, mapping the battlefield and using GIS technology is really what he's going to be briefing about, but the actual operation of that system is going to be available to be displayed, but it's only available in a relatively small room.

We originally had three groups set up that would be rotating around. Because of the time, I would like to offer an adjustment to that.

We will divide up into three groups. The members of the Board will divided into two groups. One half of the members of the Board I propose will

go to the GIS demonstration with Dr. Heller. Following that, we'll return to the Fox demonstration. The other half of the Board will start with the Fox demonstration and then will be taken to the GIS demonstration.

The other guests and visitors will have the option of going after the break to the Chem De-Mil Tour or saying here and going to the Fox demonstration.

Now, members of the Board if they want to go to the Chem De-Mil Tour, I'm certainly not going to stand in the way of any of the Board members, but I urge that members of the Board divide into two groups and there are lists that are available in the back and I can show you how we've arbitrarily divided you into two groups.

There's two vans and a bus in the back. After a short break the bus, the large blue bus, will be going to the Chem De-Mil Training Facility. The two vans are labeled 1 and 2. Group 1 will be going to the GIS demonstration and then back here for the Fox. Group 2, stay here for the Fox, get on Van 2, go to the GIS.

It's kind of complicated. I'll be available during the break to sort all this out, but

that's what I propose. And after all of the site visiting, the Board members, I believe, will come back here for the official picture. Everybody else will be free at that time I think for lunch and I hope that will get us back on schedule for the afternoon.

A recommendation for lunch is about a block over from here. Right across the street is a chapel. If you just -- if you go out the door of the theater and turn to the right and walk about a half a block, you would come to the Officer's Club. That Officer's Club has what I think is a very adequate facility for a buffet type of lunch.

So that's where I propose we go to lunch. And if there's any other plans other than that, Ms. Ward, maybe you can talk about that. But it's going to the Club for lunch for the buffet is the request.

Questions?

DR. KULLER: What do we do now?

COL. BRUNDAGE: Right now I suggest that we adjourn, go through that door to the men's and ladies' rooms and take a coffee break for a bout 10 minutes or so. And then at about 10:15, we will break into the three groups. The bus will go to the Chem De-Mil Tour. Other people will go right

through that door and you'll see the Fox vehicle. And then the third group will get on Van Number 1 and go to the GIS demonstration.

(Whereupon, a recess was taken at 10:00 to conduct site visits, followed by the luncheon recess.)

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AFTERNOON SESSION

(Time noted: 12:55 p.m.)

DR. HELLER: Good afternoon. I'm Jack Heller. I work for the U.S. Army Center for Health Promotion and Preventive Medicine, and I'm going to talk a little bit about the work that we've been doing in Kuwait for the last four years, the actual monitoring we did over there, some of the modeling we've done on exposure to oil well fires, and what we would like to do in the way of some efforts in expanding our efforts at looking at exposure of Persian Gulf veterans for various compounds, vaccines, et cetera, and building a future deployment medical surveillance system that can more effectively look at troop exposures.

In May of 1991 we were tasked by a Tri-Service working group to go over and look at oil well fire exposure to troops. We didn't want to get into the situation we did with Agent Orange and not have a good handle on what troop exposures were. And everybody assumed that the greatest environmental exposure there would be oil well fire exposure.

So, we spent from May 1991 until early December monitoring oil well fire exposure at eight

sites in Kuwait and Saudi Arabia and collected over 4,000 environmental samples, both air and soil through that time frame, including a month of background data after the oil well fires were extinguished.

But as I said, we were looking at eight locations in the Operation Desert Theater. It was about 888,000 square miles.

The risk assessment methodology we used was the EPA method for a superfund site. These were U.S. troops, so we treated the oil well fires like they were a large superfund site and we used the same methodology you would to determine if a site needed to be cleaned up and posed a risk to either on-post residents or off-post residents with a military installation.

Our conclusions were that the excess cancer risk -- this methodology gives you a predicted excess cancer list like one in a population of a million -- that the excess cancer risk was within U.S. EPA standards and the non-cancer risk slightly exceeded U.S. EPA standards. And for non-cancer risk, you're basically looking at all the compounds and comparing the level to a reference dose.

And the biggest risk driver accounting for

that 99.9 percent of the risk was non-cancer effects from benzene. So, the exposures, depending on where the troops were located, ranged from 2 to 5 times above the reference dose for benzene exposure.

This is the Desert Storm theater of operation, those four large green boxes. And as you can see, four red dots in Saudi Arabia were our locations there at King Kallid military city in Riyadh, Dhahran, El Jubail, and then we had four clustered around Kuwait City and Dhahran where a large majority of troops were at the Amani Hospital, which was about a half a kilometer from the oil well field fires, one at the U.S. Embassy and one at the Kuwait Military Hospital.

In the wake of the Persian Gulf mystery illness, two public laws were passed; 102-190 and 102-585. 102-190 is the one that mandated the formation of the troop registry, and that's being done by the Environmental Support Group at Ft. Belvoir. They're currently going through thousands of unit logs, xerox boxes, to try to determine for every troop that was in operation Desert Storm, when that troop entered the country, where he was his entire time on a daily basis and when they left theater.

We worked with them in setting up their database and it will be compatible with our GIS system to be able to look at oil well fire exposure relative to troop location.

The other public law basically talks about doing scientific research from the troop locator system.

We call our system the Troop Exposure Assessment Model, or TEAM model.

I apologize to the Board. They came over and had a little tour of our GIS system, so they've heard a little of this before.

These are just two of the investigative committees that I have briefed, that have looked at our work, and that I think have responded favorably to it.

As I said, this is just a quick look at our system. It's a geographical information system, Unix based. it has a large differential jukebox that has a storage of our satellite imagery for all the days of the war. It will also store all the environmental data that we have and the troop registry, once that comes in. And we'll be able to query on any day, any troop, to be able to look at potential exposure to oil well fire exposure.

We're working with the National Oceanic and Atmospheric Administration. They are performing the modeling for us. They have divided the Desert Storm theater of operation into 15 kilometer grid squares and there are about 40,000 of them in the field of operation. And on a daily basis, using the oil well fire emissions from the eight fields and the composition of the eight fields, they are predicting what oil well fire emissions concentration will be, and we will use that in conjunction with the ESG database to predict potential exposure and risk.

We are also using as a backup which you will see, satellite imagery. There was a satellite that would pass over twice a day and we have those images. So we're using the both of them to get our plume extent boundary. We also have, as I said, our 4,000 environmental samples. And we're using the toxicity data and the EPA database as the IRIS, Integrated Risk Information Database and the HEET, Health Effect Exposure Tables, and using a lot of their exposure data. Amount of skin surface area that would be exposed in the normal course and respiration breakdown on a daily basis. And we have modified this to meet the longer work day a troop would have and the higher respiration rate they

would have. So we have modified their data to more closely model a military situation.

This is what we will basically get out of the system. We will get a cancer risk prediction and a non-cancer risk prediction based on the reference dose standard.

The sample sites. We have inhalation risk, because we did our air modeling and we also looked at the dermal exposure and incidental ingestion of soil pathways. As I said, while we were there, we did staged soil collections to see if emissions coming from oil well fires were indeed building up in the soil and that would potentially affect the troops.

What we found in our staged sampling is there was no build up in the soil matrix of oil well fire emissions. Basically, there were almost no organics left in that sand, whether it be the temperature or what. We found very low organic concentrations. Almost nonexistent. The highest concentrations of organics obviously were in the air. The only thing we found in the soil were metals and a lot of those being, we believe, natural and refined based metals.

The two that we know were associated with

the fire, nickel and vanadium, which would have been emitted, we did not see a build up in those. So we concluded that there wasn't a great build up of particulates. So when we do our modeled risk, we'll just be looking at the inhalation pathway because the public law says what is the exposure and risk from oil well fire exposure.

This is just a look at how the GIS system works. It spatially and temporally relates various exposures and databases. In our case, we have our plume boundary. We have the troop movement under that. What I'll talk about in a minute is other potential exposures we would like to look at and integrate into the oil well fire exposure. And then we have the Desert Storm theater of operation. And you do a query. And where there's an intersection of troop exposure, you can calculate a risk. And you can do a query in any number of ways: asking for troops that had an oil fire exposure above this level; asking for the troops that had, by number of day, an exposure of 20 days or more. So there are a great number of ways to query the system once all the information has been loaded in.

Just real quickly to go over how we arrived at the extent of the oil well fire plume. This is a

modeled plume outline. Each of the dots is a 15 kilometer square grid. And so doing the modeling you get an outline of an oil well fire plume for a particular day, such as this.

This is a digitized plume. A digitized plume of this particular day's oil fires. And so we digitized that plume in; overlay the two plumes. And whichever has the greatest extent, the modeled or the digitized, that is the outline of the plume we used for that particular day to see if a troop was under it and they have had exposure.

And then to be on the conservative side, as all risk assessments are, we put a 15 kilometer buffer zone outside the plume boundary for the day.

And this is just for seven Julian days, a particular troop moving through the Desert Storm theater of operation. We did a pilot project to see if our algorithms would work and the system would work. And as the first day obvious is under the plume, the second day he's in the buffer zone, and indeed a risk was calculated for that day. And for the two days he was outside the plume at the bottom, no risk was calculated. So if a troop is not under the plume, he will not have a risk calculated for that day. And the N square just goes to that seven

days where that particular troop moved through the theater of operation.

As I said, we're hoping by December we will get the ESG database. Right now they're working as hard as they can. That's the build hold up. Until we get that with troop locations, where troops were, for how long, their relationship to one another, it's going to be very difficult obviously to do any queries.

We then have to work on the final reporting of the results to Desert Storm veterans. What we'd like to do is do some linkages to other databases, which I'll talk about. And our expected completion date is April '96.

As you can imagine, once we get the locations of 695,000 troops, that's a lot of different potential queries to run, but one obviously we have to run that we're mandated to run is what is every troops total risk for time in theater of operation during Desert Storm.

What we have is our expanded mission or our Persian Gulf War Health Tracking System. This is what we would like to do and what we're trying to develop now, resources allowing.

We had some discussions with Health Affairs

in April '95 and they expressed interest in us expanding our efforts, accelerating our TEAM effort and making it happen in a quicker fashion, incorporating other databases, incorporating a lot of the medical outcome databases, such as the CCEP database. We can take that data. We can take all the troops in the CCEP base, see where they are in their time in the theater, see if there's any relationship, if there's any grouping. We can run the group against any number of the symptoms we have. So we want to incorporate, again, medical outcome databases and then use this GIS as a nuclear to look at future deployments.

This is basically the list of databases that the NIH Technology Assessment Work Group, all of the groups who have been looking at exposure have talked about that we need to look at. And what we propose to do is go to a lot of the sources out there and basically do a feasibility study to look at the potential for how good this exposure data is going to be and then report back at one time to Health Affairs to discuss would you like us to go on with this data base; this is the quality of the data and this is the kind of information we can get out of it.

Just recently to cite an example, we got the database for batox and anthrax, such as it is, and it's basically a hand receipt that was carried over to the Gulf Region and who got particular lots of those vaccines.

Now in some cases, the group getting the vaccine, a particular medical group, annotated who they then gave those vaccinations to. So that data will be easier to use. We'll be able to say a particular group got the vaccine. You won't know if everybody -- I don't think we'll ever know if everybody in a company got it or if they got multiple shots or just one. But it's a start to at least see if someone has claimed they have gotten an exposure to one of those vaccines if they are indeed on the list of a group from the hand receipt that potentially received those vaccines.

So that's one of the databases we're working on. Particulate matter exposure we have in a lot of our air samples. We have a thousand particulate measurements in the region.

So we have a lot of other data that we think we can add to look at potential exposures on a spatial and temporal basis once we get the troop movement database.

The other thing we'd like to look at, as I said, are potential medical outcomes. Again, discharge diagnoses, the CCEP diagnoses or symptoms. All the people, if they're in there, we can track. We can look at associations between these various groups. There's a lot of what we think are information on outcomes that different people are looking at and we can take that, incorporate it into the GIS system and again, look for associations; look at where troops were and in what time frame and if there's any relationship.

This is just basically how the system works with the GIS at the center. We have our environmental exposure measurements and modeling. We have our troop movement database. And we can do any kind of queries against that. Again, when we get the medical databases, that can be related to exposure, to location, to time. And any kind of questions that an epidemiologist may come with, we can do an analysis of that data.

And the GIS has we think a lot of potential for looking at exposure and medical outcomes. And so what we would like to do is have this two ways; a real time and a -- not a stagnant but a system that sits before deployments to give medical threat and

countermeasure information. We'd like it to be able to relate on a real time basis real relative exposures to commanders. I'll talk about that a little later.

We'd like to use the Kuwait TEAM and the Persian Gulf Health Tracking System basically as a nucleus to do that.

The two big things we need to get obviously when we're looking at any troop medical outcomes are better procedures for tracking and capturing track movement. And I think we have, with global positioning systems, the technology to do that. I just don't know how far we've gotten for the next deployment to be better able to track our troops. And again, determination of exposures in medical outcomes.

As I said, what we'd like to do is historically, working with the CINC's, having them prioritize their countries of interest, their particular areas of interest, looking at, before there's ever a deployment, potential medical threats. There's a lot of information in the literature and various international organizations that have incidences of disease, historical incidences of diseases, where vectors are in a

particular country, how that is affected by altitude in a region, by rainfall in a region, by time of year in a region.

And all of this can be mapped out a head of time on a historical basis using the GIS system so we can see what the potential threats may be when troops move to a certain area. We can map historical environmental contamination; areas where there are power plants; areas where there are nuclear power plants. All of this is just information dependent. The GIS system lends itself to troop -- to overlays of troop locations, overlays of tactical maps.

And again, in a historic perspective, we want to be able to use it for medical countermeasures, to look ahead of time what the threats are and then when the actual deployment goes on to get actual real time data to assess real time exposures and potential medical outcomes to troops.

We have an organization standing up at the CHPPM. It's a FORSCOM organization. It's called the TAMIL, a theater area medical lab. And they will go out in deployments and they will be collecting disease surveillance information. They will be doing actual environmental monitoring. They

will be collecting samples. They will be analyzing samples and able to feed this information back real time to potentially look at exposures troops have in the field.

There are a lot of data sources out there that we think already have information that we can use to build our system. The Army Topographic Lab, Defense Mapping Agency, the Joint Warfare Analysis Center. For medical data we have AFMIC. We've had talks with AFMIC about sharing the information we have. There's WHO. There are DoD systems for exposure data. Again, we would rely heavily on the TAMIL for AFMIC for the PDA teams that potentially deploy and look at health outcomes in a region and look at environmental outcomes.

We're looking for, as I said, prioritizing with the CINCs. It's a large system so it has to be done in a priority system to look at what areas they think are most important, both from a medical perspective and from a geographic perspective. And again, we'll be mapping political boundaries, climatology, historical medical data, environmental exposures.

What we want to do is do a test bed to try in a limited geographical area to see how the

deployment medical surveillance system will work, see if we can monitor more closely what potential environmental exposures are, what medical outcomes are at troop clinics, in regions when there are deployments.

These were some of our potential areas: Again, in Kuwait, because we have so much information and we have a good rapport and working relationship with the Kuwaiti government. Korea, the National Training Center at Ft. Irwin, Ft. Polk or Ft. Hood.

What we've decided on -- this is just quickly. These are just basically some of the things we would look at in the deployment medical surveillance system and be able to map historically different types of diseases, vectors of diseases, potential BW-CW threats if they were prevalent in a region.

Again, we would be looking at environmental media, environmental contamination, air, surface, ground water, potential sources, elements of concern being what particular chemicals, heavy metals/organics, and the potential soldier exposure routes and what potential risk outcomes.

What we've chosen as our test is the 3rd

Army in Kuwait. The 3rd Army regularly deploys troops to Kuwait. They are moving their main installation from the Doha Peninsula to the deep water port area which is in a more industrial area. And I've requested that we do soil and air monitoring to help site that installation in the most environmentally sound area. And while they were doing that, we asked if they'd be interested in participating as a test bed for our deployment medical surveillance system to get the troops that deploy into a system that would look at potential health outcomes that would be reported in the clinics over there and look a potential environmental exposures.

We have very good contacts from the time we spent over in 1994 with the Kuwaiti Ministry of Health and the Kuwaiti Ministry of the Environment. They've been very forthcoming in sharing information with us on disease incidents, on use of industrial chemicals, on geographic distribution of vectors of disease. So we feel doing it in Kuwait and working with the Kuwaitis will make the system go a lot smoother and a lot faster. They have also volunteered to help us in our monitoring efforts and our analysis efforts.

And so this work is going to start in early FY 96, the monitoring efforts and the troop medical surveillance.

And finally, from the first meeting of the Presidential Advisory Committee on Gulf War Illness, these seem to be recurring themes that we think our system can help respond to. You know, what is DoD going to do in future deployments; are they better off now than they were in 1991.

Again, a lot of interest in the availability of the troop locator system that ESG and we are doing here. Again, assessment of environmental exposures. That theme came up over and over and linkages of environmental and medical outcome databases.

That's all I have for my prepared remarks. If we have an questions, I'd be happy to answer.

DR. ASCHER: Mike Ascher. Does this then -- does ESG and the TEAM database then become the definitive record of service in the Persian Gulf?

DR. HELLER: I would think it would be but I'm not, I'm sure, the right person to ask. But I would think that's the best record. It's drawn from all the records that came back. As I said, the thousands of xerox boxes. I don't know of anybody

that would have anything better than that.

DR. ASCHER: We were told at one point that the data on who actually served in the evaluation of the Gulf War illness were not readily available and it was a database that needed to be established. This looks like a very valuable asset if that's indeed what you have.

DR. HELLER: I think so. I think it will be.

DR. ASCHER: If it gets used for that purpose. And I'm curious is this then linking to the Persian Gulf syndrome initiative to compare the actual service versus the individuals in their registry. In other words, are all the individuals on the registry actually have evidence of service in the Persian Gulf?

DR. HELLER: I don't know. That's a very important question.

DR. ASCHER: The other thing, you say in here in the beginning -- and I'm a little confused -- about reporting your results back to the Desert Storm veterans. Now, I don't see any analysis component after you get your databases created, and I'm just curious if this is something the Board could really help with.

DR. HELLER: It probably could. One of our concerns is the public law says you will report to the veterans.

DR. ASCHER: What does that mean?

DR. HELLER: I'm not sure it's clear in the law and we have a concern like that. I mean, I don't think it's useful to say to a particular veteran, this is your excess cancer risk and this is your hazard indices. What does that mean to him? Because I don't think there's been a lot of guidance from the Congress or anybody on how they would like this information reported. So one of the things we are very concerned about and we need to work on or work with yourself, what is the best way to report this information; how it should be looked at. And so we are open to that. There is no guidance on. It simply says you will report results of exposure to Desert Storm veterans.

Does that mean when we get the thing we run a data tape on everybody and just send out a risk report?

DR. ASCHER: No.

DR. HELLER: I don't think that's clear what we really do. And that's the guidance we need. We will not take that upon ourselves to just do

that. We need the guidance.

DR. ASCHER: I think it's very clear that from the very first presentation on your part of the story I believe was in Norfolk where the Gulf War maps were overlaid with the oil plumes that there was a clear aggregate view that troops and oil were -- some were affected and some were not. And I think you should get some aggregate statistics together. I know we'd like to look at them before you start reporting individual results.

And this morning, one of the questions to your group was what is the spectrum of distribution of exposure.

DR. HELLER: Right.

DR. ASCHER: And that becomes very important because we don't like to see some kind of a graded response before we expect any biologic response.

DR. HELLER: Right. And what is -- I made the comment what is exposure. If someone was in Dhahran and the plume happened to go over there for two days, in our system that will record as an exposure, albeit small exposure. Right.

And we can query the system on number of days of exposure, intensity of exposure. So we can

do that when somebody asks a particular question. We can look at all different gradations of exposure or lengths of exposure or intensities of exposure.

DR. KULLER: I think we talked before the long history and the need to have a linkage between where the troops were, where the environmental exposures supposedly are and what disease or lack of disease individuals has. It has been a critical problem for a long, long time.

And I think developing this system is more important in reality than the interpretation right now of what data is going to come out of this because I think it's unlikely that given what we know so far, that there'll be a tremendous change in the interpretation of the data. But what may come out of it if the system works is a way of monitoring a large military population.

Especially I think your emphasis on being able to identify potential hazards prospectively before troops are sent to various places and a better idea of where those hazards are going to be, both in terms of chemical as well as biological hazards, would be very, very useful.

As I think I've mentioned to you before, I'm concerned about the fact that previous

experience on troop location has not been very good in terms of reproducibility of the data and I think that it's very important to be able to document whatever information you get is reproducible and that if you try to get it again you get the same result.

It's not that they tell you -- it's easy to say where the troops are. It doesn't say the data is correct unless somebody can show, if you give them the same data and do it all over again, finally you get the same result. Otherwise, it's just a bunch of numbers and nobody knows whether they're real or a fantasy.

DR. HELLER: They're doing a tremendous amount, almost 100 percent QA/QC on this data. They're almost doing it twice to ensure that the right data gets there and no one is missed. So they're doing a lot of -- at least on the data they have a lot of QA/QC in the collection and the data entry is checked twice.

DR. KULLER: Let me just tell you that, as I mentioned again, in Vietnam when this was done, the CDC basically went back and blindly changed all the names. Didn't change names, but basically went back and asked people to redo it again about a year

later and there was no reproducibility and that's when things got very worrisome.

So I think for your benefit it would be worthwhile to put through, when you start getting names and locations and things, just take a sample and put them back through again.

DR. ASCHER: But Lou, is that self reporting you're talking about?

DR. KULLER: No, no. This is from the same --

DR. ASCHER: The troop records?

DR. KULLER: -- the same troop movement records. It was much harder I think in Vietnam than it is in Saudi Arabia I would think, but reality is that you need to make sure that what's documented is where the troops really were. Especially your approach which is not only looking at them over a time period, the troop movement, but you're looking at a little dot. And it doesn't take much to move that individual in or outside of that circle. Might make it a smaller or big mistake.

DR. HELLER: Well, part of the thing, as we said, this is the centroid of a unit of 150 people. There is a spread on that. There are people that may not have always been with their unit. We may

have a point one day and three days later, well, where's the middle one. And so there's going to be a lot of -- what they're going to try to do, as Jeff said, is a lot of data fill to try to get that. We may never get that data or accurately get that data and just have to make guesstimations about locations for particular days.

DR. KULLER: One of the other things you might want to do, which again was done in the past by several groups in the Vietnam experience, was to query the troops or soldiers, what they think they were exposed to and where they were versus the database. And again, that produced very, very poor correlation.

DR. ASCHER: Well, that was my point. Because in our report on the Persian Gulf Syndrome, that's already been done. And 68 percent of the 10,000 have recorded oil well fire. It will be very interesting to cross index just to see, because as you all know for all your good effort with computers, if this gets into the political arena the answer that will win is the self reported answer, even though you have good science behind you.

So I think the sooner you can cross validate that questionnaire against your

environmental assessment, the better off you are. If you find a discrepancy next week, better rethink what you're doing.

DR. HELLER: And what is considered oil well fire exposure? What does a troop consider oil well fire exposure --

DR. ASCHER: Right.

DR. HELLER: -- versus what we would measure as an exposure.

DR. ASCHER: That's right. And if they work together, great. But if you have a big difference in terms of what people are reporting on questionnaires versus what you find they actually were, you'd better go back to the drawing board because, as I said, the one that will win is the self reported.

DR. KULLER: Well, whether it wins or not, I think the reality is that it what happened in the attempts to do the Vietnam experience studies was the fact that they could not match up. They could match up the fact that the soldiers were in Vietnam and roughly how long they were there but they could not match the exposure, supposed exposure to Agent Orange with what the troops really thought they were exposed to, nor unfortunately could they match up

the datasets that get repeated about where the individual units were. And that's very, very different than the Saudi Arabia experience because they were looking for individual units. There was some real concern about how close they had to be because it was not a -- you have a fixed source environmental exposure. They had essentially obviously a continuum exposure and a mobile source of exposure, so it's a different situation.

But I think the main thing is that this model is so important for future evaluations that it's important to make sure that you can document that the techniques you're using are reproducible, as well as the fact that you can get a point estimate of what exposures are and a point estimate of where the troops are. But anybody could do that but you're throwing darts. We've got to make sure that your system is better than throwing darts.

DR. BROOME: Just to follow up on that a bit, has the form and the process for troop location identification been modified at all due to the process or is this sort of just standard military procedure? Has there been any attempt to improve the accuracy of the troop locator documentation?

DR. HELLER: All I know -- there was to be

a group set up to look at a better -- because comments have continuously been made about we can't keep going through xerox boxes. I don't know how far that has really gotten to doing a better job of looking at locating troops.

I know some letters have gone out and there's some interest. But beyond that, I don't know how far it's extended. And every time we give a presentation we talk about we've got to develop a better way to whoever we speak to.

DR. BROOME: Because we also commented during our earlier discussion that it's not just a matter of where they were but also some indication, particularly from respiratory toxins, of their activity levels and which were resting, which were actively engaged in maneuvers, whatever, would be very important for these kinds of exposure modeling approaches.

DR. KULLER: Thank you very much.

We're going to move on to the typhoid vaccine issues and I guess that's Captain Warren.

LTC. FINDER: I want to take a few minutes just to introduce the next speaker, who's Captain Todd A. Warren, who, by the way, is no relationship to General Warren A. Todd. It's been hard for me to

keep his name straight.

But before I introduce Captain Warren and talk about typhoid, I want to do a little bit of a commercial.

This is for the PEC. For some of you who know about the PEC and those of you who don't, very quickly let me tell you a little bit about what we do, how we got started, and also a little primer of pharmacoeconomics.

Very quickly. I'll try to go through this very fast because I don't want to take away from typhoid. Plus, we were told that we only had 45 minutes but I guess now we have more time, so we can take.

No? Maybe not.

DR. KULLER: We'll see.

LTC. FINDER: I could talk about this for hours.

Very quickly, this is the goal. We're trying to reduce total health care costs.

(Laughter.)

That's actually the goal of preventive medicine to reduce total health care.

Here is kind of where it got started. I don't want to take much time. But as you can see,

this is the cost for MEDCOM alone, MEDCOM. And this is one of the things going back in the '80s. It was going through the roof. We can't account for all the reduction in cost for pharmaceuticals in MEDCOM, though I think if you look at things like drawdown, changes in the inflation rate and here and there, you still see a large percentage that is not accounted for, and we take credit for some of that.

I'd be happy to show you the business plan if you had time, but we can actually show the amount of dollars that we've saved in just direct cost.

The point is we've had an impact but that's not really what we're here to talk about. The point is this is what we got started for.

The PEC is a DoD level agency. It started off as an Army organization and then the Air Force and Navy kind of got involved early on and joined up and DoD Health Affairs got involved and now we are a DoD organization and the Army is the executive agency.

And just to kind of show you some of our new missions, there's been a major change in the way pharmacy is being -- policy is being set up in DoD and this is some of the missions that the PEC has taken -- is now in charge of, to include the TRICARE

oversight. And the bottom is the pharmacy prescription database that right now apparently involves about 10 million prescriptions in the database. Eventually, every prescription written in DoD either at TRICARE or far as CHAMPUS or in the MTF's will be in this database. That's still years out still.

Now, very quickly, a quick primer just so everybody has an idea of what we're talking about, pharmacoeconomics. It's very straightforward. And what we were talking about this morning, for example, the malaria, it goes along the same lines.

This is really what we do and this is what pharmacoeconomics does. You basically frame a question and we look at the entire disease state. We don't look at whether one drug is cost effective or not. We look at whether what is most cost effective way to treat a particular disease state, be it typhoid vaccinations, being not really a disease state but kind of a disease entity of its own. Or entity is maybe a better word. And then we develop a model, we figure out the approach. You can read it. I'm not going to read it to you.

Very quickly. And this will all make sense as we go through typhoid.

Very quickly, some definitions, just so everybody understands what we're talking about.

Cost benefit is what is normally done out there. It's generally been the state of the art. Cost effectiveness is a new process where you don't -- step back for a second. Cost benefit, you try to value everything in a monetary term, which means you're trying to value how much is a life worth or how much is a day of work worth. And cost effectiveness, which is what we do, we don't try to value those things. We set up a model that looks at the amount of dollars it costs to perhaps improve reduced blood pressure or the typhoid model to save a day of work in the field. And you'll see that in the analysis.

It's not -- and there's some advantages and disadvantages but that's beyond what I want to say here. The point is that cost effectiveness is one kind of analysis. Cost benefit is another kind. And the cost benefit analysis tends to be, for these kinds of problems, very difficult to actually do.

And this is some of the issues that we put into the models and is it chronic or acute. In typhoid it was neither, but we're looking at multiple doses. In typhoid some of the vaccines are

multiple doses and one of them is not. So we look at all these issues.

And the bottom shows you the kinds of analysis we do, whether we do it with a decision tree, a Markov analysis -- and again, it just means that there's many different methods that can be used and we try to make sure we use the right one for the right disease.

And this is just some of the information that goes into the models. We look at all the probabilities. And this information, by the way, comes from the medical literature whenever possible. What we try to do is we try to have objective data for every -- everything goes into a model is based on some sort of objective data. In most cases, if we can find the literature, we find it. And we go through hundreds of articles. In some cases we can't find it because a lot of the stuff just isn't out there. Compliance is a big issue we just can't find. There's not a lot of information on compliance in the medical literature.

But we did try to do things in other ways. Looking at databases, for example. Looking across the military. What is the compliance or what are the treatment failure rates across the military.

When it comes down to when we can't find the literature and we can't find it through any kind of a database search or things like that, then we oftentimes go to consensus panels of experts, which is, as you all know, one of the weakest forms of evidence.

Very quickly, I'll just show you them model, the general model we have. It's very straightforward. There's some sort of an effectiveness measure which is the denominator. This can be the percent reduction of blood pressure if you're looking at blood pressure. In the case of typhoids, we have actually two models and Captain Warren will talk about the effectiveness measure. This is what we're trying to find, trying to maximize, if you will. And the top is the cost, the cost of treating the disease or in this case doing the vaccinations, any side effect costs that are an effect to the military.

If a patient has a side effect like upset stomach and they stay home and they take some Mylanta, that doesn't really cost the government anything, so we only look at costs that are incurred by the government. We have a very focused perspective, being this is the government and this

is the health care system's perspective.

We look at things like failure costs and opportunity costs. And you'll see that in the model.

So without any further adieu, I'll go ahead and introduce Captain Warren.

Captain Warren is a pharmacist. His pharmacy at the University of Nebraska was working through the PEC about the middle of February as a clinical pharmacist rotation at Wilford Hall at the same time the Defense Medical Standards Board asked us to please look at the issue of typhoid, the oral vaccine versus the one-shot vaccine. And so he was here and he took on the responsibility of doing that analysis.

CAPT. WARREN: Thanks, Dr. Finder.

What I'd like to do the next few minutes is spend time talking about the actual analysis which we did on the typhoid vaccines. It was a pharmacoeconomic analysis to determine which vaccine was the most cost effective.

I'll flash a little side up here with some history numbers on it.

The thing I want you to notice is between the Spanish-American War and World War I was when

knowledge that good field sanitation would improve typhoid. And also it's the time the typhoid vaccine was invented and mandatory vaccinations of troops occurred.

So World War I and thereafter, typhoid did not make that much of an impact, whether it was improved field sanitation or the vaccine could be difficult to determine.

I just want to flash a summary of some of the currently available typhoid vaccines, the first of which is typhoid vaccine USP. You've got a handout on this.

As I was saying, typhoid vaccine USP has been around for quite a while. It's a vaccine that's given initially twice after 28 days. It's also the cheapest. It costs 90 cents.

Next on the market was Vivotif. It's an oral vaccine. It is a live type 21A wholesale vaccine. It's got a complex dosing schedule. It's given once every other day for a total of four doses, which occurs over a time period of a week and it costs just over $2.00.

And last to enter the market this Spring was Typhim-VI. It's a cell subunit vaccine. It's the VI-capsular antigen and it's also the most

expensive vaccine but it has an advantage in that it's given once initially as an IM shot.

I just want to flash up the current CDC recommendations. They do include the military, for military folks who are deploying to an endemic area, and then of course, travelers.

I'll flash up the preventative measures slide, not to tell you what they are because I know you all know, but to relate to you the way we felt in their importance to our project, because none of the currently available typhoid vaccines have 100 percent efficacy.

Most review articles that we looked at and most of the experts that we talked to will tell you that typhoid vaccines generally have a 70 percent efficacy, and 70 percent is the number that we used in our analysis.

The next slide is going to show you some side effect incidents. In the past this was a very big issue, especially with typhoid vaccine USP. And before that, the military used fairly widely an acetone wholesale vaccine which had even more side effects associated with it.

Vivotif, which is the oral live cell vaccine is associated with virtually no side

effects, and the newest vaccine on the market, the Typhim-VI, is associated with a much decreased side effect profile over the old typhoid vaccine USP.

A unique issue to the Vivotif is its complex dosing schedule, which brings to point a compliance factor. There have been two published studies which have looked at the compliance rates or how well somebody is taking their capsules to Vivotif, and it was found that between 70 and 80 percent of travelers -- and you have to keep in mind these were motivated travelers in the study, will be compliant.

We talked to several people in the preventive medicine fields in the various services and most felt that this compliance factor was probably below 50 percent. For the purposes of this analysis, we used the number 65 percent to give the benefit of the doubt.

Another unique issue with Vivotif is because it's a live vaccine, the manufacturer recommends that it be taken 24 hours after completing any antibiotic regimen. The CDC recommends that it be taken 24 hours after completion of prophylaxis with mefloquine.

If for some reason you have a troop, a

sailor or airman who has to be vaccinated before deployment, you have a dilemma, because mefloquine is dosed once weekly. You start a week before you leave or as soon as possible before and the Vivotif, it's regimen lasts seven days. So you're going to have one of two problems. Either you're going to have a delay in the deployment of that person or you're going to have a delay in the protection of that person against malaria. And most of the typhoid endemic areas are also going to be endemic for malaria.

Just briefly, to reiterate what Colonel Finder already went through, this is the methods that we used in this analysis. First off we did an extensive literature search to come up with all the articles we could find which had been done on typhoid vaccines, including review articles, articles on the efficacy of the vaccines, articles which looked at side effects. And there were a couple of articles which had already been done on the pharmacoeconomics of the vaccines.

Colonel Finder alluded earlier to the mathematical models. This was a rather unique proposition for this pharmacoeconomic analysis. Most pharmacoeconomics is done via a decision tree.

When deciding how to go about coming up with our models, we had a dilemma, so we ended up coming up with two mathematical models.

The first one is what we call the standard model. This pertains to personnel who have not yet deployed to an endemic area for typhoid fever. And the second model we called the deployment model. This pertains to those personnel who have actually deployed to an area which is endemic for typhoid fever.

The standard model is going to give us a cost effectiveness ratio which will compare the total costs which are associated with a vaccine and compare those costs to the number of cases of typhoid which were averted with that vaccine. And again, it pertains to those personnel who have not yet deployed to an endemic area.

This is the actual equation. The ratio on the top is what is the answer. It's going to give you a dollar figure per person or per case of typhoid averted, so it may be $20 per case of typhoid averted versus another vaccine, $30. It costs $30 to avoid one case of typhoid fever.

Let me just go through the variables real quickly. Cost of the vaccine plus all the costs

that go into administering the vaccine -- alcohol pads, cleaning the guns used to administer the vaccines and so on. Then we have the sum of all the side effects which might occur and the costs which the government would incur in treating those side effects; the efficacy of the vaccine. Next is the compliance rate for the vaccine. This was only if Vivotif had a compliance factor which was less than 100 percent. The attack rate for typhoid fever and the costs incurred in treating people who actually acquired typhoid fever.

And on the bottom, in order to get the number of cases avoided, it's the efficacy, the compliance and the attack rate of the disease.

The deployment model has a little bit different ratio in the answer. It's going to calculate the total costs associated with a vaccine and compare those costs to the number of manhours which were saved when that vaccine was used. And again, this applies to those persons who are actually deployed.

Just leave that slide up there.

The only difference in this equation between this equation and the standard model is on the bottom. You'll notice we have in parentheses

hours lost. This is what we estimated would be the average number of hours for someone who actually acquires typhoid fever.

Once we set up the mathematical models, we noticed how many holes we had, how much data we were lacking to actually complete the analysis. So the sources of data which we used, we went to the medical literature, of course, for efficacy, side effects data. We got some attack rates from the literature. We went to the Federal Supply Schedule, DPSC for cost used in the vaccines, the cost of equipment, and medications used to treat side effects in typhoid fever.

We went to AFMIC to try to get some data on typhoid attack rates in the world today. We went to the history books, looked at the historical data on typhoid fever. We talked to various individuals in preventive medicine departments in the three Services, and I may have talked to some of you in the audience.

The various personnel centers in the Services and also the Defense Manpower Data Center were good sources for demographic data.

We talked to various immunization clinics among the three Services to find out how they

actually administered the vaccines. If they had the oral vaccine, did they have patients come back to get supervised dosing or did they not.

With all pharmacoeconomic models you have assumptions which are built into your model. Our model assumed all persons vaccinated were U.S. military personnel. We did this from the point of view of the U.S. Government, not the individual vaccinee. We included only the initial vaccination in this analysis for several reasons.

Number one, it's difficult to determine how long someone will remain in the Service. The average is under four years. It's difficult to determine how long somebody is going to remain on a deployable status and also if you do a pharmacoeconomic analysis which occurs over a period of years, you have to take a discount factor for each year the analysis occurs, and it basically would nullify the results that we would get from this analysis because it decreases our dollar figure so much.

We also assumed that if you're in a deployment situation, your health care personnel costs would be nil, because those personnel are already there whether they're working or not. And

also, laboratory costs would be the same. It would cost the same to perform in the field as they would back here in the United States.

Again, I already mentioned the compliance rate we used was 65 percent for the Vivotif and the attack rate that we used was 2 percent or 20 cases per thousand. And that was a figure that I got from both review articles and I got that figure from AFMIC. And that was the highest attack rate that I could come up with in the world today.

This slide just summarizes the results which we obtained from the standard model. A couple of points to look at. Number one, how can you have a cost associated when they don't even get a vaccine. A cost associated with no vaccination comes from those people who've acquired typhoid fever. Therefore, you have a cost.

Typhim-VI emerged as the winner for two reasons. Number one, it does not have any factors which decrease its efficacy; i.e., compliance. And also it has a fairly low side effect profile.

Now the old vaccine, typhoid vaccine USP, is associated with a lot of side effects and that's the reason that it has such a high dollar figure is the cost of treating its side effects.

Vivotif, which has the lowest side effect profile has the compliance problem. Therefore, you have more people who are going to acquire typhoid fever. Therefore, it's cost was above that of Typhim-VI.

The results from the deployment model were similar, except that no vaccination became almost the most costly. The reason for that is in the deployment model we included the costs associated with lost work and so no vaccination is going to yield the most cases of typhoid fever and therefore, that's what raised its cost.

The way we came up with zero as manhours saved per vaccine is if you don't get any prophylaxis, you're not going to save any hours. And that's how we based the manhours saved with the other vaccines.

I want to flash this slide up because it gives you an idea of the variables that went into our analysis. The only one that's not up there is the efficacy rates for the various vaccines. And I showed you a slide with those earlier.

In the analysis, once it's performed, what we do is a sensitivity analysis, so we plug these numbers in individually from the bottom end of the

range to the top end of the range and then collectively to see if those numbers are going to change the results of the analysis. And that's what's known as a sensitivity analysis.

The next slide is going to give you an idea what that looks like when you change the typhoid fever attack rates. The blue line is no vaccination and this pertains to the standard model. If you notice, at about 3 percent on the attack rate, no vaccination becomes less cost effective than vaccinating with Typhim-VI. And as you approach 10 percent, even the old typhoid vaccine USP becomes more cost effective than no vaccination at all. And again, these are all based on dollar figures.

The next slide is going to show you what happened when we varied the compliance rate for Vivotif. Keep in mind that at no time in the analysis did Vivotif become the most cost effective vaccine to use because there's a cost associated with having someone go to an immunization clinic to have a supervised dose. So each time they go to take a capsule, if you want to shoot for 100 percent compliance there's a cost in lost work.

With this slide, we ignored that lost work cost or that opportunity cost and these are the

results. You have to a approach 80 percent compliance with the Vivotif in order to make it the most cost effective vaccine to use. And there may be situations where you could do this. For example, in basic training. That lost work could be contributed to a preparation cost.

The major costs that are going to be associated with your typhoid vaccines are not the acquisition costs of the vaccine. You saw where Typhim-VI costs $5 to acquire or to give one shot in acquisition costs versus the old typhoid vaccine USP at 90 cents. It's not the acquisition cost that accounts for your major costs. It's not the cost of administration. It's the cost of treating side effects, and that's the cost of treating those people who go on to acquire typhoid fever.

Again, as I just touched on earlier, when you ignore the opportunity costs associated with a supervised Vivotif dosing schedule, it does become cost effective if your rate approaches 80 percent. Otherwise, it never was the most cost effective vaccine according to our analysis.

A factor which greatly affects the overall cost for typhoid vaccination, of course, is the typhoid fever attack rate. At low rates, cost per

people who acquire typhoid fever are negligible. When the attack rates are high, then your costs are going to be quite substantial. The take home point is anything that's going to affect the efficacy of your vaccine, like your compliance rate or your improper storage of the vaccine is going to impact your total cost because it's going to decrease the efficacy of that vaccine.

For the military, the cost effectiveness or vaccination may not be the only determinant. In military readiness, there are many issues that need to be considered and cost is but one of those. And again, with the military, your perspective is important. You may be looking at a small unit where typhoid fever may be devastating to the effectiveness of that unit, whereas if you look at the whole organization which the small organization may be part of, it may not hurt the unit at all, or that small unit may be like a Patriot missile battery. It may impact the organization as a whole.

Typhim-VI with -- let me go back.

One of the things that we found during the analysis was that it is not cost effective to immunize troops who are not on a deployable status. So one of the ideas we had was if you could

accurately predict the typhoid fever attack rate for certain endemic areas, it may be possible to immunize on a deployment by deployment basis. The data that we obtained from AFMIC would not make the possible as of yet.

Typhim-VI would be the most ideal vaccine to use if you're vaccinating on a deployment by deployment basis for a couple of reasons. Number one, it's one shot. You can ensure compliance with it. And also it does not interfere with any of the other prophylaxis which may be going on, like mefloquine.

In conclusion, Typhim-VI emerged as the most cost effective vaccine in most instances that we looked at. And again, immunization of personnel who are not in a deployable status is not cost effective.

Again, I want to stress the preventative health measures. None of the currently available typhoid vaccines offer 100 percent efficacy. Therefore, the preventative health, good field sanitation is essential.

Vivotif, if you can give it in a situation where you can negate the costs of a supervised dosing schedule, it is possible that it could be the

most cost effective vaccine only if you can guarantee 100 percent compliance. Vaccine that you give to personnel, of course, who aren't on a deployable status, consider that to be a waste.

The recommendations from the Pharmacoeconomic Center to the Board are you should not immunize somebody against typhoid fever unless they are considered to be in a deployable status or a deployable billet, and that would have to be determined by each of the three Services.

If the capability is out there to predict, accurately predict the typhoid fever attack rates, then you should immunize on a deployment by deployment basis. If the endemic area does not meet a certain percentage, i.e., 3 percent, then it is not cost effective to vaccinate personnel entering that area. And if you do -- if it would be possible to immunize in this manner, than Typhim-VI is the only option to use.

And then again, our recommendations for Vivotif, if you can give it in an environment where your lost opportunity costs can be negated or ignored, like a basic training environment, then it can emerge as your most cost effective vaccine and only if it's given so that all your doses are

supervised and you can count on 100 percent compliance.

That concludes my presentation of the analysis. Is there any questions?

DR. CHIN: Dr. Chin. When you tried to calculate the attack rate, was that the attack rate of the endemic population or is that sort of an estimated attack rate of what the military personnel deployed there might have?

CAPT. WARREN: It was an estimate.

DR. CHIN: Of what?

CAPT. WARREN: Of the attack rate which the military personnel would incur when they enter that area.

DR. CHIN: Given their observation of the environmental precaution? That is, if they observed the environmental precautions.

CAPT. WARREN: That is something that we couldn't determine.

LTC. FINDER: Can I point out one thing? In the entire Vietnam War there were only 62 reported cases of typhoid fever. There was probably four million people in Vietnam overall, maybe more. And the vaccines only have a 70 percent efficacy. So based on those numbers, you would have expected

many more cases. Granted, there was, I'm sure, underrreporting, but the point is the actual typhoid attack rate for soldiers is probably extreme low and beyond probably being actually measured.

So we had to use a number that we had to kind of come up with as a consensus number, and this was based a lot on endemic attack rates. And really the truth is, if you notice in the analysis, we did -- we let that vary. We let the attack rate vary because the problem was we did not know the attack rate. No one really knows the attack rates. And one of our recommendations in the actual paper, which we have copies of and we can pass around, is that there ought to be some sort of intelligence looking at what the real attack rate are to make these kind of recommendations because the attack rate is a critical piece of information.

DR. CHIN: My major point is that you could try to calculate perhaps what the attack rate in the endemic population is but that would not necessarily and probably is not the attack rate that you expect in terms of the military, the U.S. military that are deployed there if they follow the precautions.

LTC. FINDER: Oh, absolutely. Personally, I would have gone even farther. I would have said

we don't give typhoid vaccination at all. Let's just do preventive measure; field sanitation, good water hygiene.

DR. CHIN: That gets me back to why you go through all this modeling.

LTC. FINDER: Well, the modeling though shows that. It shows that the attack rate is less than about 10 percent. You know, 10 cases in 1,000; that there's no benefit to it whatsoever. The question is, no one really knows what the true attack rate is. We just don't know that.

CAPT. WARREN: That's part of the reason that we did the sensitivity analysis. We went from .002 percent all the way up to 20 percent.

DR. CHIN: But you used 2 percent, though.

CAPT. WARREN: Yes. We used 2 percent. But when we -- the only change that we had --

LTC. FINDER: We didn't use 2 percent. We used .2 percent. It's 20 cases per thousand.

Never mind. Never mind. It's too much complicated for me. You're right. Never mind.

DR. ASCHER: We had this discussion on the cholera vaccine for deployment to Africa, and the question was based on one commander as to whether the troops needed cholera vaccine. And very quick

back of the envelope calculation said if they follow the recommendations for sanitation, the risk is zero. Therefore, the answer was no. It's the same argument. And a highly endemic situation where the population was running much higher than 2 percent. So you can't use the population number. Jim's point, I guess.

DR. WOLFE: Dr. Wolfe. Two points I'd like to raise. One is that with all three of these vaccines, if you wait until deployment, leaving within a couple of days, these vaccines really don't offer protection until about 14 days, all three of them. So that's a point to consider when you're waiting for immediate employment to give any of these vaccines.

The other point is that I think we maybe have talked about this with other vaccines but the retention factor of whether troops are going to stay in for more than two years. If they are, if you can get around the cost of administering Vivotif, it becomes much cheaper because of it's five year protective efficacy.

DR. ASCHER: The recent discussion we had where we really could have used your help -- and perhaps you'd go back and do it for us, is the

hepatitis A issue. There's some situations for the use of hepatitis A where you get really gray, and particularly versus ISG. And we could use your help in the day care unresolved issue. We could use your help in the cost effectiveness versus a globulin, because that's going to go up for bid. Globulin is a big problem nationally in terms of availability. Do we really want to have it any more? How does that play out?

LTC. FINDER: Can I just make a couple of comments? I don't mean to steal your thunder.

The first thing is we're not the ones who make the recommendations on whether we should be vaccinated or not. I mean, that's what -- at least I feel what the AFEB does. We're providing the data. And I think one of the pieces of data we're seeing is that the attack is a very critical piece of information. If we don't think the attack rate is very high, why bother to vaccinate. We weren't really quite ready to make that call because it's not really our call. So we're here to give you some information.

COL. BROWNE: Why did you use as your base case attack rate a rate that wasn't even reached in Vietnam or Korea or World War II?

CAPT. WARREN: Based on the graph which was part of the sensitivity analysis, that is the current attack rate for the Continental United States.

LTC. FINDER: The problem is -- here's the problem we had to deal with. No one knows what the attack rate really is and the big difference between the attack only -- let me go back to the slide. This may explain somewhat what the issue is.

What you're seeing here is that the real issue with attack rate is whether you should immunize at all, so we did go back and look at attack rates like 2 per million or 2 per hundred thousand, whatever that .002 is. And what we're saying here is that the attack rate, only when you get to about .3 percent or 3 percent do any of the vaccines become actually at all cost effective compared to no vaccination.

Now, the truth of the matter is, regardless of what the attack rate is, the relative difference between the different vaccines, between Typhim-VI versus the oral vaccine doesn't really change much either. The point was we just picked a number that we kind of were able to get, kind of a consensus number from AFMIC and staff as to what they thought

kind of what the attack rate is, knowing full well that that is not really the real attack rate.

We had to pick a number because we had to do the analysis. You just can't leave it at zero as an attack rate because then it doesn't matter. And then we did the variant. We varied it here to see what would happen at different levels. And what this plot is telling you is that as it gets lower and lower, there's no reason to vaccinate. But that's not our call. Our call was to do the analysis.

I'm not trying to put this on someone else's shoulders. It not that we don't want to do that. It's just that I think this is a call of the AFEB to decide is the attack rate of typhoid such that we ought to vaccinate. And my personal opinion is it should not be done at all. We don't need to vaccinate.

DR. KULLER: I think there's one other part of this which I would call -- a little bit of a difference that I might call tolerance limits rather than a sensitivity analysis. I think this is fine and I think it's very nice from an abstract issue. But you have to turn it around the other way because I think what you have to do is look at the cost in

relationship to other costs. Everything costs something.

The question would be what's the tolerance limit of acception of typhoid fever cases in the military given a deployment. For example, if you deployed 100,000 troops someplace and you got six case of typhoid and two of those cases died from typhoid, is that an acceptable tolerance limit with a vaccine which costs X dollars, you might be able to prevent those two deaths. Can you go back to congressman X and say because it cost X dollars to immunize with typhoid vaccine we decided not to use it and therefore, this poor soldier who was from your district died.

LTC. FINDER: Sir, that's a political question which is well beyond the scope of this kind of analysis.

DR. KULLER: I don't think it is. I think in dealing with these issues, when you have a vaccine which is available and the vaccine is safe and the question becomes not only -- I mean, I'm not disagreeing with your analysis because I think it's very good, but I think that you have a tolerance limits analysis here and that is the analysis of cost effectiveness in relationship to what other

costs, what else to use the money for. In other words, it's not a matter of how much does it cost. The question is what else do you use the money for that you have. And what's the tolerance.

I mean, my view of life would be to say the tolerance of typhoid and the essentially severe morbidity from typhoid might be zero. We went through with encephalitis in the past where you had one case of encephalitis that caused a national catastrophe.

So one of the problems that occurs in these kinds of modeling -- and I'm not sure what the answer is and you don't know either, and none of us do. But I think in making a decision about whether you do or don't use a vaccine which is safe and efficacious and is available, you have to really set the tolerance limits. And as long as you're up front in doing that and saying we're willing to accept the reality that we'll have a rate somewhat to Vietnam, given good sanitation and good X and Y, without doing immunization. We're willing to accept the rate of .04 per thousand which is pretty low and it's pretty remarkable and it's very good. And we'd all sit around the table and say that's phenomenal success.

Unfortunately, if you deploy a couple of hundred thousand troops and end up with six or eight cases, one of them could be a catastrophe.

LTC. FINDER: Of course, the flip of that is even if you give everybody 100 percent vaccinations you may still have one or two people die from typhoid.

DR. KULLER: But unfortunately in the real world, it's like a surgeon operating on somebody that's got an X lesion. If the patient does poorly, the surgeon could also ways if you didn't have the surgery you'd been even worse.

LTC. FINDER: Oh, I understand. I understand.

DR. KULLER: If you didn't have the surgery and did badly, you'd be up the creek.

DR. HANSEN: How many died in Vietnam?

DR. KULLER: I have no idea.

DR. HANSEN: Well, this doesn't say any died.

DR. KULLER: But how much morbidity is associated with the typhoid.

DR. HANSEN: But I mean, it's a really bid difference between morbidity and death. And the point you're making is deaths. And these data don't

show --

DR. ASCHER: Well, he said his analysis can't use the years of life lost and all those other factors. It's not that kind of analysis.

LTC. FINDER: Well, we could have done that but that's really a different kind of analysis and that's actually fraught with problems.

The bottom line is you're right. Someone said this is reality and you're absolutely right. This is reality. But what we're dealing now with is two kinds of issues here. One kind of issue is a resource allocation issue, which is really a much larger scale, and then the other issue is more of a narrow focus; should we allocate resources to this issue.

And the analysis pretty much says what is says, based on the attack rates, based on the compliance rates, that there may not be a benefit to this particular issue. Now, in a perfect world where there's unlimited money, it's not an issue. In a world where there are legal liabilities and congressmen, it may be an issue. I don't know the answer to that.

DR. KULLER: And I think your analysis and the method of using it is excellent. I think the

problem is one has to carry that forward. I think this is a beautiful way to carry it the next step, and that is to say that we can't -- theoretically can't prevent everything. And what you're doing is modeling the best preventive approaches, but have to face the reality that something potentially can happen.

LTC. FINDER: Two other quick points, if you don't mind. This will finish the questions.

The first thing was the point you made about deployments and not everybody gets deployed has time. And one of the points we made in our discussion was that it depends on the situation. Many people deploy and they have plenty of time to deploy. I mean, it may take a month to get some units. Some of these units that were going to Desert Storm took two, three months to get over there. They knew they were going. In that kind of situation it might work perfectly fine. If you've got a ready reaction team that's going to be deploying in 24 hours, I would say immunize those people up front. It's just something that has to be determined.

And then the third thing is hepatitis A. We have another Air Force resident who just started

two weeks ago and who's actually doing hepatitis A, and actually she's talked to a few people in this room already.

DR. ASCHER: We'd like to see that very much. Thank you.

DR. CHIN: I don't want to beat a dead horse but my main point was I recognize it's difficult to estimate a typhoid attack rate. My specific question was, was that estimate of the attack rate in the endemic population. And you realistically cannot take that, if it is for the endemic population. You cannot take that rate and apply it to the military. You have to try to estimate what you think the rate would be in the military. You can make it high if you want but it has to be realistic.

CAPT. WARREN: I agree with you and that was an issue that came up in the analysis.

DR. CHIN: But my question still is that 2 percent, is that the endemic population or what you think the attack rate would be in the military?

CAPT. WARREN: That's what we felt the attack rate would be to the military.

LTC. FINDER: No, no, no. Let me explain because that's not quite the right answer.

No, no. Here's what we did. We looked at what was available out there; what the research was. And the first thing we realized was no one knows what the attack rate was. No one knows. We called AFMIC. They didn't know. We called people in preventive medicine. No one knew.

So we were stuck with the dilemma. So the reality is we picked a number and we picked a number higher than we thought it would be because we figured what we really wanted to show -- and this is what this graph is all about. We wanted to show how the results change as the attack rate resolved. But change it. We just picked a number. We could have picked 50 percent. It would not change the mathematical model itself. We could have put .01 percent. We didn't know if we picked a number. Two percent seemed like a fairly ubiquitous number out there.

But what the point was doing the sensitivity analysis or the tolerance levels, if you will, are what we used to look at this. And we know that 2 percent is probably pretty high. And so we're saying listen, if at 2 percent it's not cost effective, then we know that it's not going to be cost effective at a more realistic number of .01

percent. And it wasn't based on what we thought was the attack rate for the endemic population, though that was one of the things we looked at.

Does that answer the question better, sir?

DR. KULLER: We have a question over here.

LT. COL. PARKINSON: One of the things, Steve -- appreciate that presentation. One of the things that reminds me a little bit of Homer Simpson's philosophy on where he's going to cut out some money from his family budget, and he turned to Marge and said, you know -- he said, we need to cut out those shots for Maggie. They keep giving her these immunizations for diseases she never gets.

(Laughter.)

But carried to its illogical extreme, we could probably not immunize against anything because the attack rates for all of the things we're talking about are so low, fortunately, for other reasons.

But what this brings to this discussion -- and I'd like to just flip it back -- is two things. First of all, most of the immunization recommendations that are coming out of ACIP nowadays because we do have lower attack rates, they're based on indirect cost calculations; absenteeism from work, mothers staying home, those types of things.

And I think we have to start folding those into our calculations more directly in DoD because with a 24-hour day operation, worldwide global thing, single mothers, families, that type of stuff, saying that it doesn't save us direct medical care dollars but it saves the line a tremendous amount of indirect what's called line dollars.

And I'll talk a little bit tomorrow about how we're working on breaking down this dichotomy between the DHP budget and the line budget, which is an artificial barrier. And this methodology reflects it because you're already saying, well, that's not a medical cost. That's why we don't put it in our calculation.

Those are the very things that should be folded in at some level. And to think about that issue.

The second thing is, getting back to Dr. Kuller's point. All these things, you know, the cost of this is against a background of what we just heard is a multi-million dollar system, with no good health outcomes, no good exposure endpoints. And what is the cost per case of lung cancer prevented under that system that we're looking at for the smoke plumes? I mean, that's kind of a relative

merit of where the DHP puts dollars vis-a-vis these things.

So in terms of -- it's not so much -- you know, this can go on like an epi journal club where we talk about the methodology, but you guys should be complimented for bringing this issue here, standardizing the methodology and --

DR. ASCHER: The last vaccine recommendation we wrote is exactly on my point, which is the issue of varicella vaccine in recruits. And it was very impressive that the main factor driving the need for varicella vaccine was the logistical disruption and it was all time lost in getting people off schedule. So the whole thing was justified based on getting people through basic training in a timely fashion and those numbers overrode everything else.

You could redo that analysis after the fact in your model and come up I think with the same numbers. It might be a good way to look at it.

LTC. FINDER: Actually, unfortunately, you're only seeing part of the model here. And this is a model that was very unique. I mean, some of the other models that we did for other diseases actually rolled into this productivity loss, loss from work

time for the units.

But we didn't do that here because it was actually in the model, if you looked at the deployment model. That was the number of hours that were lost to the commander. I mean, a soldier, you know, 1,000 hour lost or 1,200 hours lost to the commander, whatever. And that's a very good point, though. And that's something that we are trying to roll in. It's a difficult one to do, though.

LT. COL. PARKINSON: The other thing that Dean Blackwood here, who's been involved with recruit medicine at Wilford Hall for years, is that he estimates right now that 70 percent of all our recruits coming through basic are going to be on deployment status. As we downsize, as we talk about total force, everybody's ready to go. So as that universe gets closer to 100 percent of the people who come in have a likelihood of going to a remote area and we control those first six weeks such that we could give them four supervised doses at no opportunity cost because our staffs are doing that anyway, you just walk up when they do their PT in the morning and pop it in their mouth. I mean, those things become factors, too.

So, we're moving towards an all deployable

force. That ratio is changing.

DR. KULLER: Any other questions?

(No response.)

Okay. We're going to -- unfortunately we can't find Colonel Leitch right now so we're going to take a break right now.

Members of the Board, we're going to meet in the Chesapeake Room in about 15 minutes. That's in the other building I think; correct? The other building. We'll meet there in about 15 minutes. That will be a closed meeting of the Board.

(Whereupon, the public proceedings were adjourned at 2:20 p.m. to be reconvened on Friday, October 13, 1995 at 8:00 a.m. in the same place.)